The study of Friedel-Crafts type reaction mechanisms

Thesis

THE STUDY OF FRIEDEL-CRAFTS TYPE REACTION MECHANISMS

A Thesis submitted to the Open University

for the degree of Doctor of Philosophy

By

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DEPARTMENT OF CHEMISTRY

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To my wife, mum and dad

for all the love and support

they have given me.

ACKNOWLEDGEMENTS

I would like to thank my supervisor, Dr. P.G. Taylor, for his helpful advice and encouragement throughout my study.

I would also like to thank the Open University for providing me with the funding and facilities for carrying out this research. Many thanks are also due to the technical staff of the Open University (Chemistry department), and in particular to Mr. P. Patel, for the help and assistance they have given to me throughout my study.

My sincerest thanks are also extended to my wife, Linda, who spent many hours on the typing of this manuscript.

DECLARATION

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ABSTRACT

In recent years the role of π and σ complexes in electrophilic aromatic substitutions has aroused much controversy. Olah has argued that the transition state in electrophilic aromatic substitution is not a fixed one. With strong electrophiles it can occur early along the reaction coordinate resembling a π complex, with weak electrophiles the tranistion state occures late, resembling a σ complex. This argument is based on a number of benzoylations and benzylations on benzene and toluene in which the electrophilicity of the electrophile has been varied. These conclusions have come under strong criticism and in order to shed light on the exact mechanism the following research was undertaken.

This study is centered around the Friedel-Crafts acid catalysed cyclodehydration of 2-benzylbenzoic acids although the cyclodehydration of 2-naphthoylbenzoic acid and 2-benzoylbenzoic acids were also studied. The cyclodehydrations were effected mainly with methanesulphonic acid, but sulphuric acid, polyphosphoric acid and trifluoromethanesulphonic acid were also employed. Rate constants were measured and products of cyclodehydration were identified for all model compounds.

The cyclodehydration was investigated by varying the electrophilicity on both the substrate and the electrophile. Consequently many new substituted 2-benzylbenzoic acids were synthesised. Hammett plots were

also made and ρ values calculated. In addition to this the deuterium isotope effect was also investigated, but none was observed. Acidity function work (H_R) was also carried out on methanesulphonic acid to try to extend the range to 100% acidity.

Analysis of the rate constants and product distributions shows that the transition state resembles a σ complex rather than a π complex. Hammett and acidity function studies do, however, indicate that the rate limiting step in the reaction is variable. This is dependent on whether there are electron withdrawing or electron donating groups present in the substrate. With electron donating groups the loss of water in the formation of the electrophile is the rate limiting step whereas with electron withdrawing groups the formation of the σ complex is rate limiting.

CONTENTS

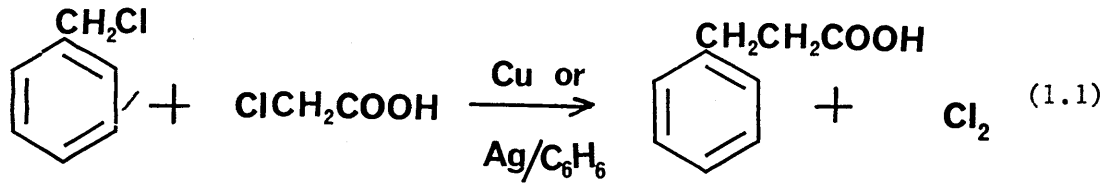
INTRODUCTION

Chapter 1 - Introduction

1. Historical Review of the Friedel-Crafts Reaction

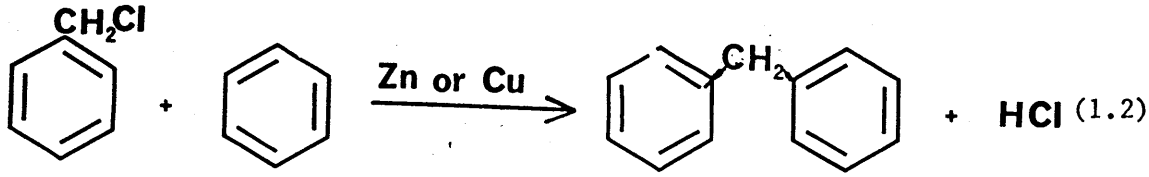
In 1877 Charles Friedel and James Mason Crafts published their first paper[1] on 'a new general method of synthesis of hydrocarbons, ketones etc'. Following a long standing tradition, the reaction that they pioneered in this work was given the name of the 'Friedel-Crafts Reaction'.

This, however, was not the first example of this type of reaction. In 1869 Zincke,[2] in an attempted synthesis of 3-phenylpropanoic acid (equation 1.1) reported the formation of diphenylmethane. The reaction was carried out in benzene solution in a sealed tube in the presence of copper or silver metal, the purpose of which was to consume any chlorine gas produced.



(1.1)

The products of the reaction were totally unexpected; as well as the formation of diphenylmethane, hydrogen chloride was evolved instead of chlorine (equation 1.2), some metal halide was also recovered.



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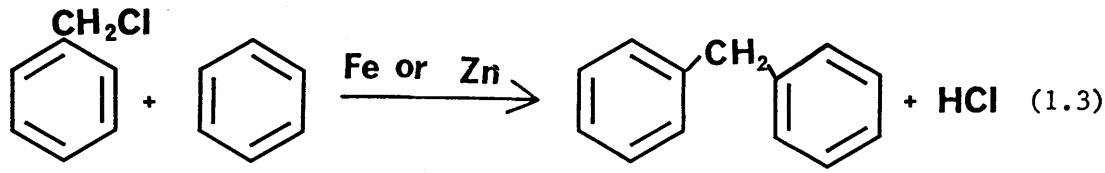
This surprising result led Zincke to study the reaction of benzyl chloride with toluene, benzene and p-xylene,[3] (equations 1.3-1.5).



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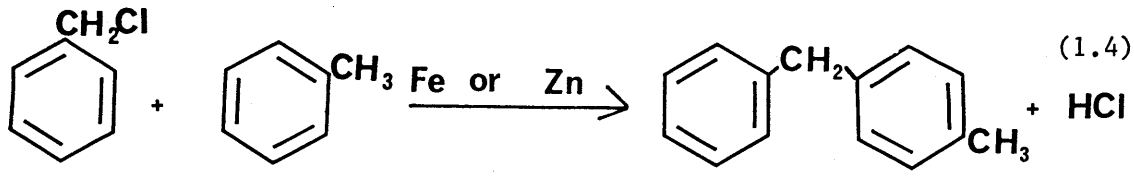

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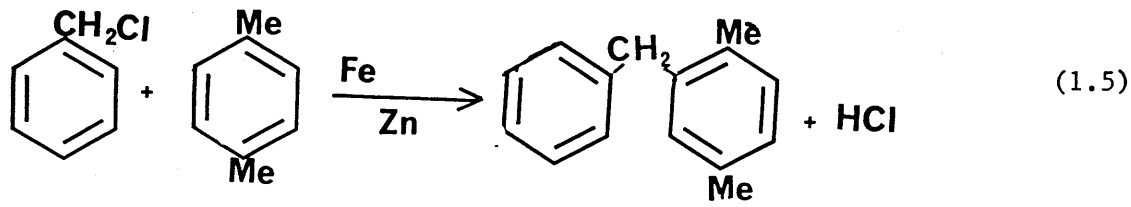
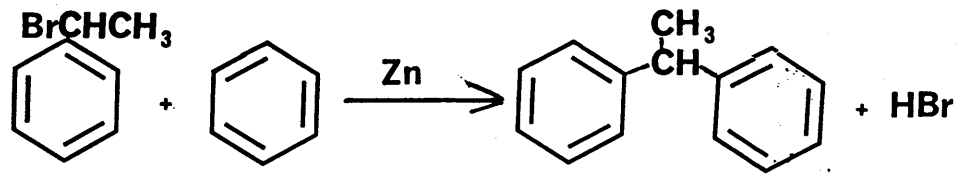


(1.5)

He found that the reactions could proceed at about 100°C in the presence of zinc or iron, however, with copper higher temperatures had to be employed.

This work was continued[4] with an investigation of the reaction of 1-

phenylbromoethane with aromatics such as benzene and toluene in the presence of zinc metal (equation 1.6).

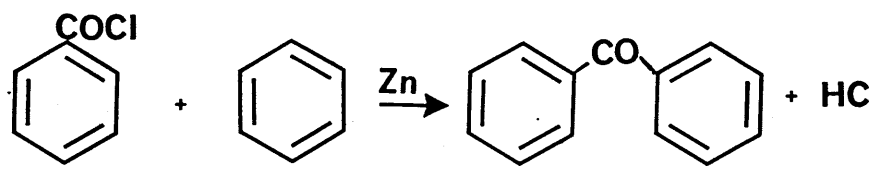


(1.6)

The products were found to be as expected, confirming the general nature of the condensation reaction.

Throughout these studies it was evident that a metal was necessary for reaction to take place and that hydrogen chloride (or bromide) was always produced. Furthermore, the final products always contained some metal halide as well as the metal. In spite of these observations no explanation was forthcoming from the authors as to the nature of the reaction.

At about this time work was carried out on the acylation of aromatics and in 1873 a paper was published entitled 'ketones from aromatic hydrocarbons and acyl chlorides'.[5] This described the reaction between benzoyl chloride and a number of aromatic hydrocarbons (equations 1.7, 1.8). The conditions employed were basically the same as those used in the earlier alkylation reactions.



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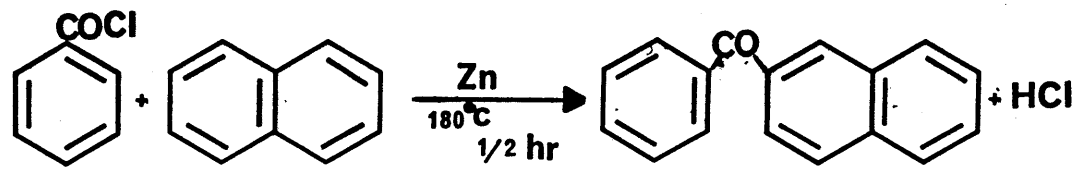

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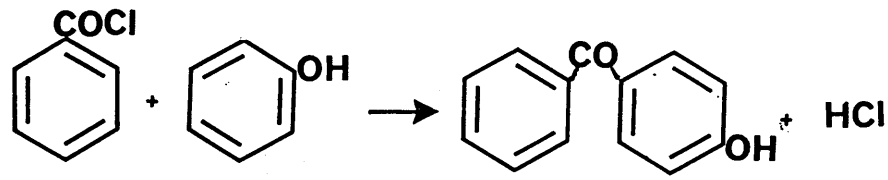
This paper also reported the formation of p-hydroxybenzophenone and a complex ketone when phenol was employed (equations 1.9, 1.10).



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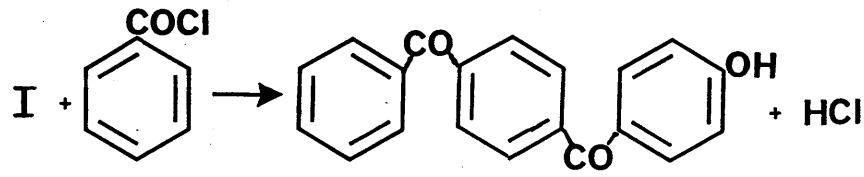
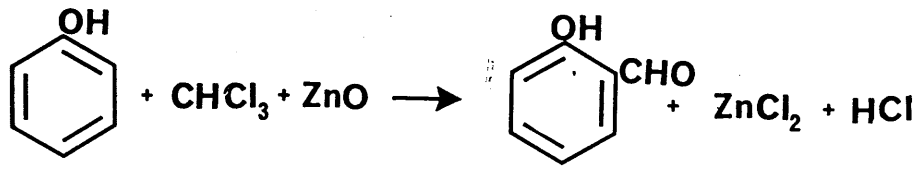


(1.10)

Whilst zinc metal was used in all the reactions no mention was made of any zinc chloride being formed, however, the evolution of hydrogen chloride had been noted.

In 1876 the preparations of salicylaldehyde and o-hydroxybenzophenone were reported[6] (equations 1.11, 1.12). These reactions were carried out in the presence of zinc oxide (not zinc metal) which was found to have been converted to zinc chloride on completion of reaction.



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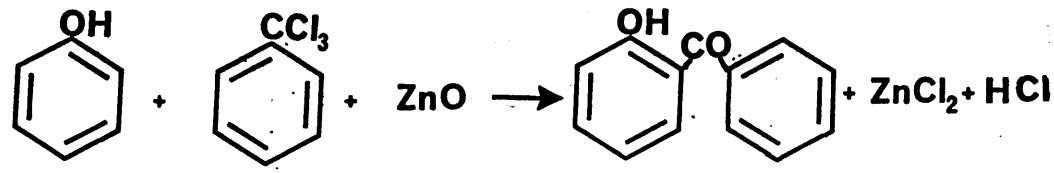
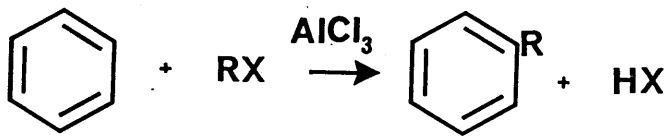


(1.12)

It was clear from all the previous work that the same fundamental reaction was involved in each case, however, none of the authors really understood exactly what the true nature of the reaction was.

Friedel and Crafts were the first to realise exactly what was happening and after a long and thorough investigation of the reaction were able to devise a reaction of synthetic utility, (equations 1.13, 1.14).[1]



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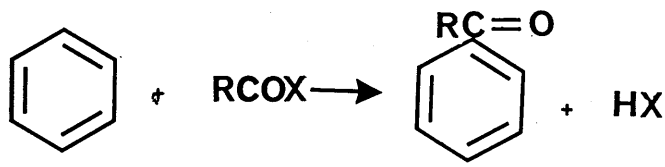


(1.14)

They found that the metal halide was essential for reaction to take place, but not every metal halide was capable of inducing a reaction. Of all the halides they tested, aluminium chloride proved to be the most satisfactory and to this day it is still one of the most widely used reagents for the Friedel-Crafts reaction.

2. Synthetic Utility of the Friedel-Crafts Reaction

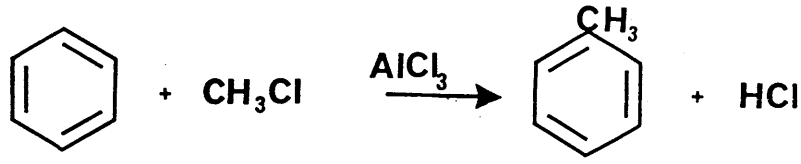
Since its discovery, the Friedel-Crafts reaction has become one of the most important and versatile reactions available to the organic

synthetic chemist. The catalysts used by Friedel and Crafts although still very important have been supplemented by a large number of other catalysts. Amongst these are not only Lewis acid type halides (eg. $AlCl_3$, BF_3, $TiCl_4$, etc.), but also Bronstead acids such as sulphuric, hydrofluoric, and polyphosphoric acid.

In general the Friedel-Crafts reaction can be subdivided into two convenient categories: i) alkylation, ii) acylation.

2.1 - Alkylation

This reaction involves the uniting of two species, one being alkyl in nature and the other being aromatic. Reaction is brought about by means of a catalyst, which can be either a Lewis acid type metal halide or a Bronstead acid. A solvent also has to be employed, but this role is often filled by one of the reactants, (equation 2.1).



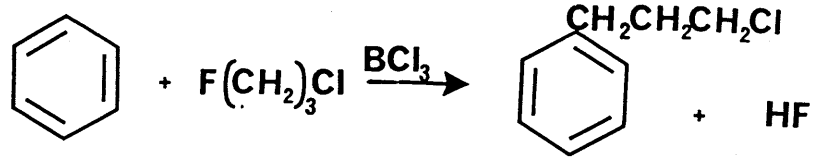
(2.1)

Here benzene acts as both reactant and solvent. It was thought that in reactions of this type the aromatic component had to be used in excess in order to prevent polysubstitution taking place, as the resulting alkylbenzene is more reactive than the starting material. This however does not cure the problem since polysubstituted compounds often form a major part of the products of such systems. The difference in the reactivity of benzene and alkylbenzenes[8,9] has been proven to be insufficient to allow such polysubstitution to predominate. It is now believed that these side reactions are due mainly to a heterogeneous

system.[10] During reaction the catalyst tends to form a separate dense layer as it is usually only slightly soluble in the solvent. This dense layer selectively dissolves the alkylated products which are then exposed to an abnormal concentration of both catalyst and alkylating agent. This finally results in polyalkylation taking place. If, however, a solvent is used, such as nitromethane, or nitrobenzene, which is able to dissolve the catalyst, this problem does not arise.

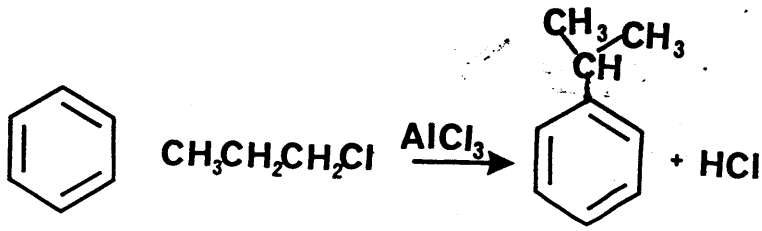
There are several alkylating agents, besides the alkyl halides. Amongst the most frequently used alkylating agents are alkenes, alkynes, alcohols, esters, ethers, aldehydes and ketones, paraffins, mercaptans, sulfides and thiocyanates. Although not all of these are as efficient as the alkyl halides.

Alkyl halides and alcohols alkylate relatively easily and efficiently. The order of reactivity for alkyl halides is F>Cl>Br>I.[11] It is therefore possible to attach a haloalkyl group to a benzene ring, (equation 2.2),[12] by means of a dihaloalkane containing different halogens.



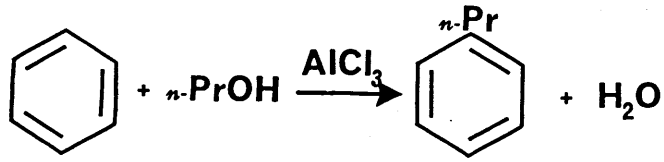
(2.2)

Tertiary and benzyl halides are the most reactive followed by secondary and then primary halides. A similar order of reactivity is observed for alcohols. One of the great disadvantages of alkylation with alkyl halides, however, is that rearrangement of the alkyl group often takes place, (equation 2.3).



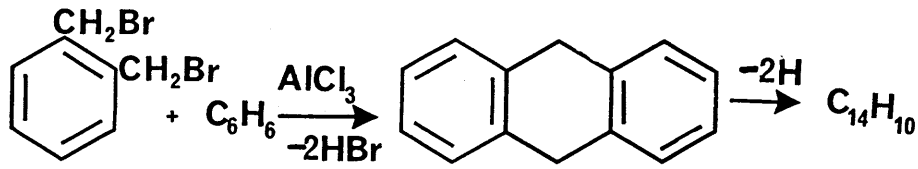
(2.3)

This problem does not usually arise if an alcohol is used with an aluminium trichloride catalyst (equation 2.4). However, with boron trifluoride and sulphuric acid rearrangement does occur.



(2.4)

Dihalides and diols can also be used as alkylating agents (equations 2.5, 2.6).[13,14]



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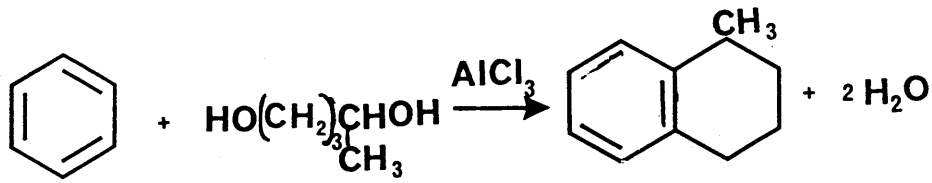
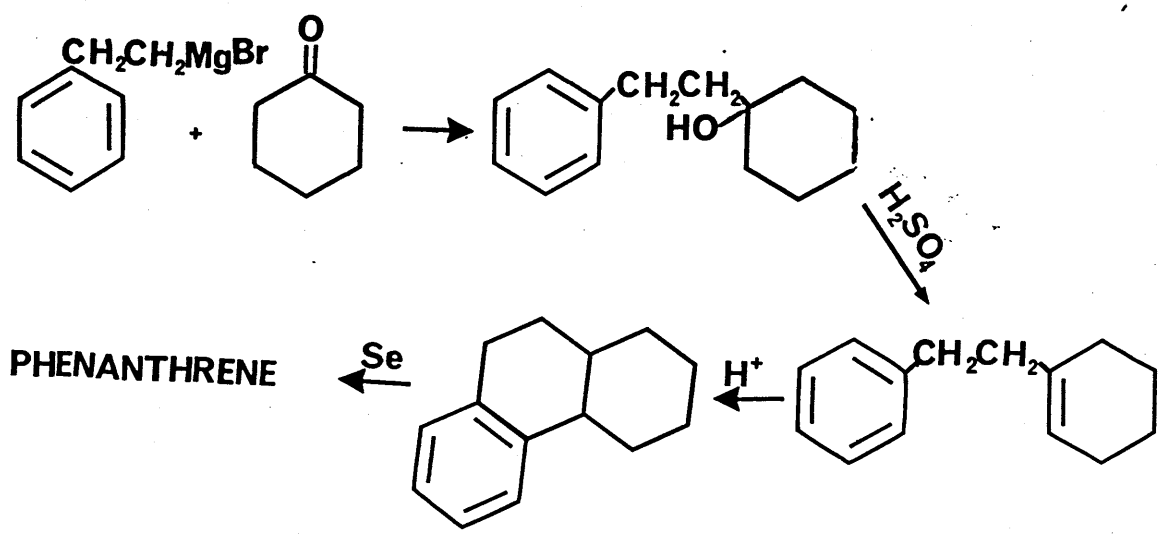


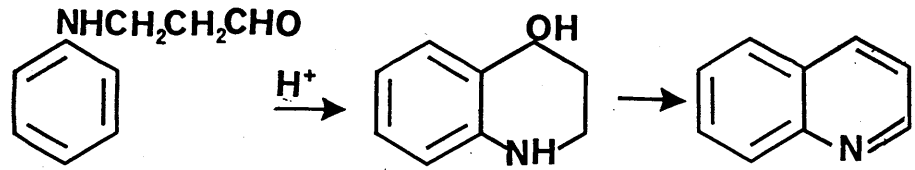
(2.6)

Other efficient alkylating agents are alkenes, ethers and alkynes. In the Bogert-Cook synthesis of phenanthrene one of the steps involves intramolecular alkylation by an olefin, (equation 2.7).



(2.7)

Ketones and aldehydes are also important alkylating agents, the Skraup synthesis of quinoline is one important example, (equation 2.8).



(2.8)

Although aryl halides cannot generally be used as arylating agents, in special circumstances they may be employed. p-Fluorophenol reacts with benzene in the presence of aluminium trichloride to yield hydroxy biphenyls.[15] Halogenated naphthalenes also react with benzene to produce phenyl naphthalenes. Friedel-Crafts alkylation, whilst being a very versatile reaction does suffer from a number of major drawbacks. Apart from rearrangement and polyalkylation, dealkylation can also occur. If p-xylene is heated with aluminium chloride, both alkylation and dealkylation take place and the product is a mixture of hydrocarbons; some with fewer alkyl groups, others with more. Another limiting factor is that the aromatic species should not be strongly deactivated to electrophilic substitution. Thus chlorobenzene reacts, but nitrobenzene does not. Even with strongly activating groups, such

as hydroxyl and amino, problems arise. Phenols react with aluminium chloride to give phenoxy aluminium dichloride. This is only sparingly soluble in the reaction medium and therefore reaction is very slow. If the methyl ether is used instead, there are no difficulties. With amines the catalyst usually forms a complex which is strongly deactivated towards electrophilic substitution. Despite these problems Friedel-Crafts alkylation has numerous possibilities and will continue to be of great importance in organic synthesis.

2.2 - Acylation

Like the corresponding alkylations, Friedel-Crafts acylation reactions also involve an aromatic substrate, and a catalyst as well as an acylating agent. The aromatic substrate has to be slightly activated towards electrophilic substitution and therefore deactivating groups such as sulphono, keto, cyano and nitro prevent acylation. The catalysts generally employed are aluminium trichloride and boron trifluoride, but others can be used (eg sulphuric acid). The amount of catalyst employed is greater than that used in the corresponding alkylations. This is because the resulting ketone complexes with the catalyst and thus removes it from the reaction system. A number of acylating agents are available and these include acyl (or benzoyl) halides, acid anhydrides, esters, or the acid itself, (equations 2.9 - 2.12).

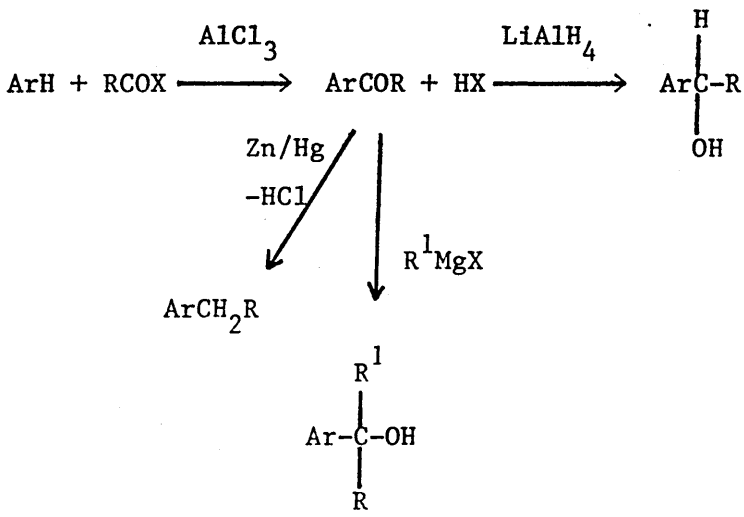
$$ArH + RCOX \xrightarrow{AlCl_3} ArCOR + HX \qquad (2.9)$$

$$ArH + (RCO)_2O \xrightarrow{AlCl_3} RCOR + RCO_2H \qquad (2.10)$$

$$ArH + RCOOR^1 \xrightarrow{AlCl_3} ArCOR + R^1OH \qquad (2.11)$$

$$ArH + RCOOH \xrightarrow{AlCl_3} ArCOR + H_2O \qquad (2.12)$$

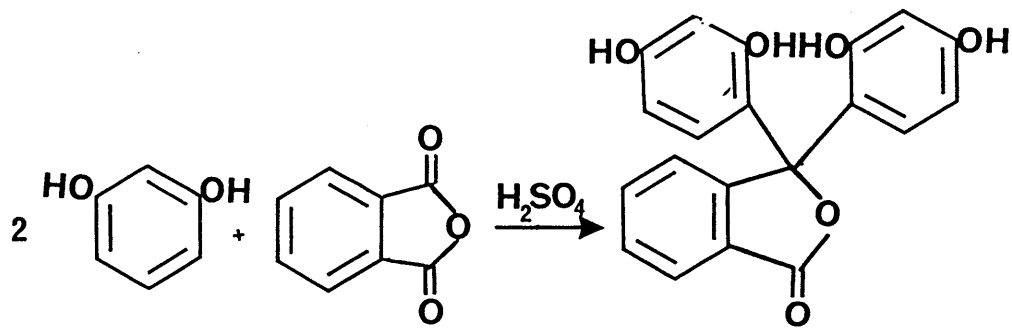
The acylation reaction is on the whole synthetically a much more useful reaction than alkylation. There are no problems with rearrangement of the acyl group and polyacylation is difficult. This is because the incoming acyl group strongly deactivates the ring to further substitution. Furthermore in an ortho-para directing system it is usually only the para isomer that is formed. This reaction is so trouble free that it is not only very important for the preparation of ketones, but also for the synthesis of alcohols and alkyl benzenes, (equation 2.13).



(2.13)

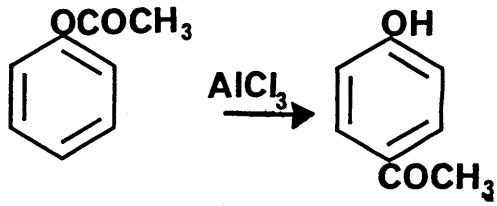
By the use of a Wittig reagent the keto group can also be replaced by an alkene group.

With very reactive aryl substrates such as anisoles and phenols side reactions are possible. Phenols react with aluminium chloride to form phenoxy aluminium dichloride; with excess phenol, aluminium phenoxide is formed. Acylations can be carried out on these derivatives by the use of excess catalyst. However, the method has serious limitations. Anisoles can, if allowed, form phenols by cleavage of the ether linkage by the catalyst. These problems can be avoided if the temperature of reaction is strictly controlled, or milder catalysts are employed, (equation 2.14).



(2.14)

Another way of preparing acylated phenols is via the use of phenolic esters. This rearrangement reaction is known by the name of the Fries reaction (equation 2.15).

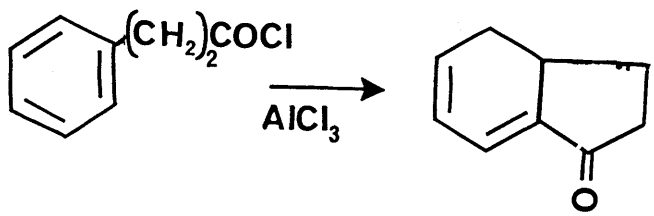


(2.15)

Acylation of heterocyclic and benzenoid aromatics is also possible. Naphthalene is very reactive towards acylation and readily undergoes diacylation. The heterocyclic systems, pyrrole, thiophene, furan and pyrans can be acylated relatively easily. Pyridine and quinoline however, are very resistant to acylation.

2.21 - Cycloacylation

Intramolecular acylation reactions form an important part of Friedel-Crafts chemistry. Ring closure can be effected by an acyl halide, anhydride or an acid. The catalysts used normally are aluminium chloride, sulphuric, hydrofluoric or polyphosphoric acid. This method can be used to produce several classes of compounds, some examples of which are given below, (equations 2.16 - 2.20).



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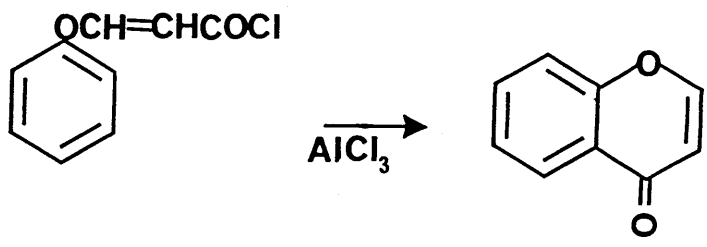

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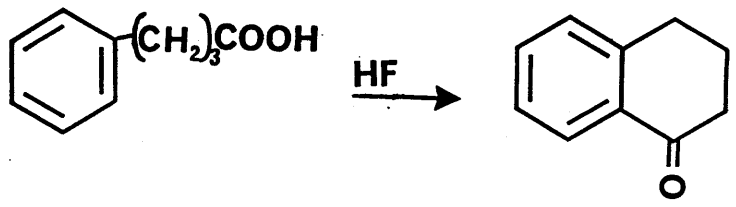

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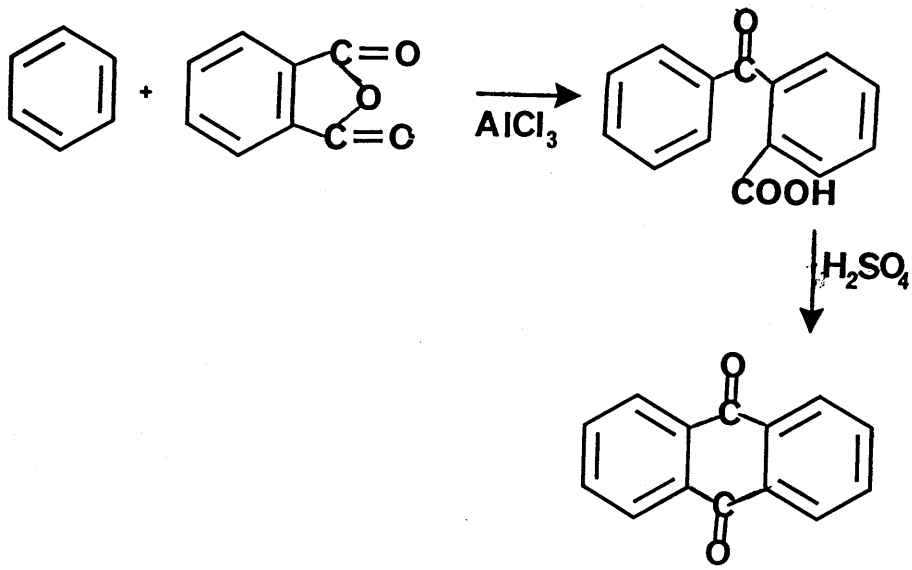

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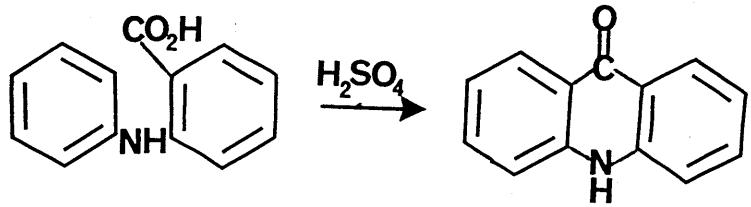
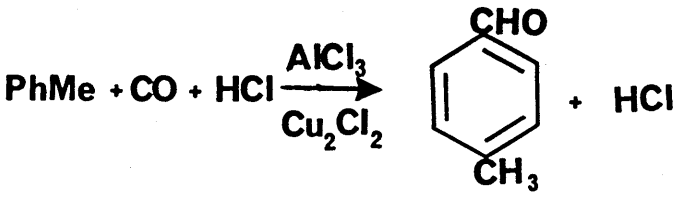


(2.20)

These reactions can be carried out very conveniently and are relatively fast. Normally room temperature is sufficient, although cooling may be necessary.

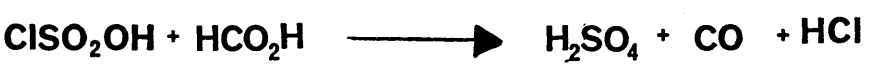
2.22 - Formylation

Gatterman and Koch[15] devised a synthesis by which aromatics can be formylated in good yields, (equation 2.21).



(2.21)

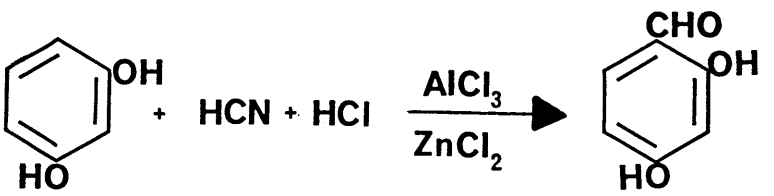
A problem with this method, however, is obtaining an equimolar mixture of anhydrous hydrogen chloride and carbon monoxide. In laboratory preparations this can usually be overcome by the reaction of chlorosulphonic acid with formic acid,[16] (equation 2.22).



(2.22)

This synthesis is suitable for benzene and its substituted derivatives as well as polycyclic aromatics, though rings containing deactivating groups cannot be formylated. Substitution is predominantly in favour of the para isomer.

Phenols and phenolic ethers although activated cannot be formylated by this procedure. A modified Gatterman reaction, however, can be used successfully on phenols and their ethers, (equation 2.23).



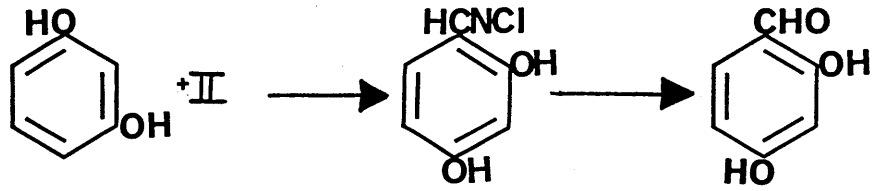
(2.23)

This method although efficient has the drawback of using hydrogen cyanide gas, but a system has been devised where the gas can be generated in situ, (equation 2.24).

(2.24)

As well as hydrogen cyanide, zinc chloride (the catalyst) is also generated. Another modified method is available where cyanogen bromide is used in place of zinc cyanide,[17] (equations 2.25, 2.26).

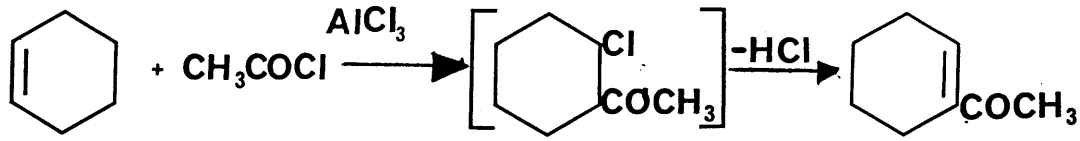
(2.25)



(2.26)

2.23 - Acylation of Alkenes

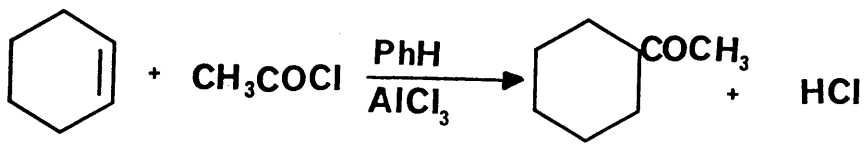
In the presence of aluminium chloride alkenes react with acyl halides to produce unsaturated ketones, (equation 2.27).



(2.27)

Other catalysts may be used such as zinc chloride, tin tetrachloride, iron trichloride, etc. The reaction involves addition followed by elimination. A saturated chloroketone is formed as an intermediate, which loses hydrogen chloride to give the acylated alkene.[18]

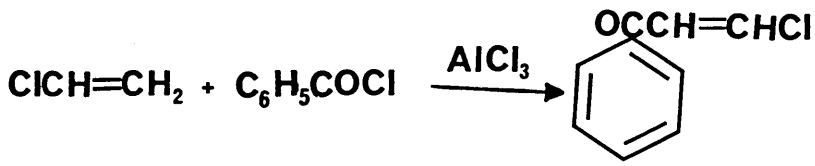
Saturated alkyl ketones can also be obtained by this method,[18] (equation 2.28).



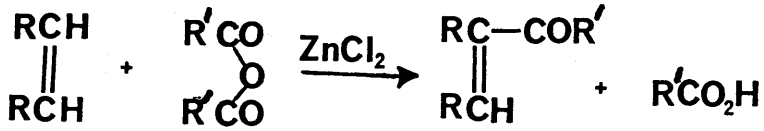
(2.28)

The unsaturated ketone is probably hydrogenated at the expense of the solvent.

Benzoyl chlorides and anhydrides can also be used as reagents for acylation, (equations 2.29, 2.30).[19,20]



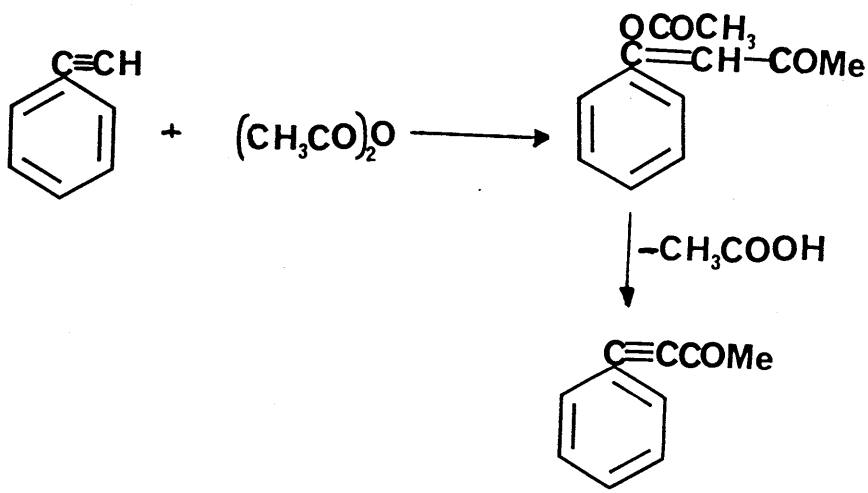
(2.29)



(2.30)

Alkynes can be acetylated similarly, although often the products are alkenes and not alkynes, (equations 2.31, 2.32).

(2.31)



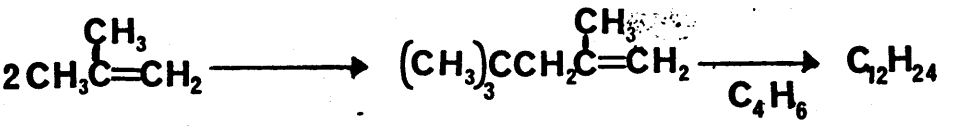
(2.32)

3. Industrial Applications

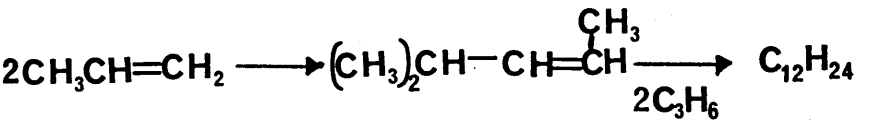
At first the chemical industry was somewhat slow in appreciating the value of the Friedel-Crafts reaction, but gradually, over the last century the reaction has become increasingly more important. The reasons for this were mainly concerned with the price of aluminium chloride. In acylation processes large amounts of catalyst were required and usually recovery of the catalyst was not possible. Obviously if the catalyst could be produced cheaply then industry would be much more receptive to Friedel-Crafts synthesis. Today several methods are available for the preparation of anhydrous aluminium trichloride[21] and this coupled with a number of new catalysts, such as BF_3 and HF, which are recoverable from the reaction, make Friedel-Crafts synthesis a much more viable option for industry.

The reaction is now widely used in the petroleum, polymer, pharmaceutical, perfume and dye manufacturing industries. Aluminium trichloride was once a very important catalyst for the petroleum industry being employed in the cracking of heavy oils to produce low boiling hydrocarbons, free from both sulphur and olefinic impurities. This method has now been superseded by newer and more efficient catalysts such as hydrated aluminium silicates, zeolites. The products from these cracking processes have to be chemically treated in order to remove sulphur or gums and to improve the colour and odour. The low boiling hydrocarbons are used as fuels in motor vehicles.

Polymerization is a relatively new area in which Friedel-Crafts catalysts have been used. Propene, but-1-ene and 2-methyl propene are the usual reagents for polymerization, (equations 3.1, 3.2).



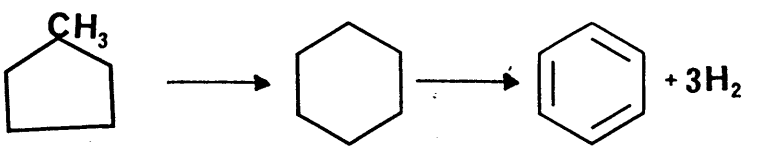
(3.1)



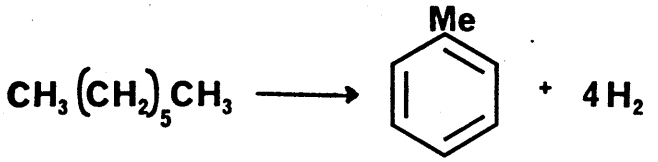
(3.2)

Polyisobutenes are used as plasticizers, for coating fabrics and for improving the viscosity index of lubricating oils. Probably the most important polymer produced by Friedel-Crafts synthesis is polystyrene. This is made by treating benzene with ethene in the presence of aluminium trichloride. A process similar to that of polymerization is alkylation and this has become a major force in the petroleum industry. Using hydrofluoric acid as the catalyst, isoparaffins and certain olefins can be converted to hydrocarbons that boil in the gasoline range and have excellent anti knock properties. These hydrocarbons now form a major component (25-60%) of the fuels used in the aviation industry.

The production of aromatic compounds such as benzene, naphthalenes, toluenes, etc. is also achieved by the use of Friedel-Crafts catalysts. The separation of aromatics from petroleum is not easy as the aromatic concentration is very low, but using appropriate catalysts enables the conversion of paraffins to aromatics (equations 3.3, 3.4).



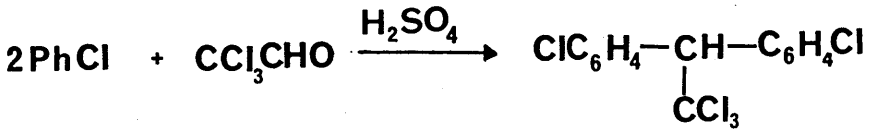
(3.3)



(3.4)

Whereas the process does not yield high concentrations of benzene, toluene and xylene can be produced in large quantities. In recent years a relatively new technique has been developed (Hydrodealkylation) which allows the conversion of toluene and xylenes to benzene. As benzene is usually cheaper than toluene this process is only of importance in the United States of America.

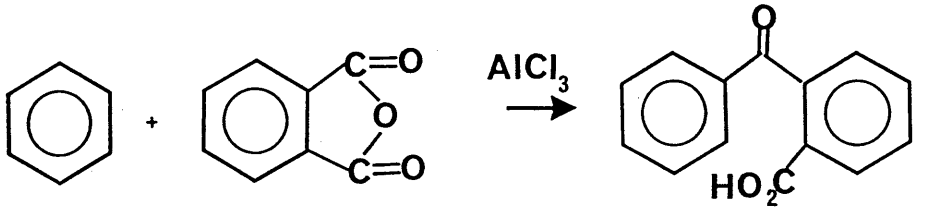
The Friedel-Crafts reaction is of great importance in the agricultural and insecticides industry. The most widely used insecticide (DDT) is prepared using such a reaction (equation 3.5).



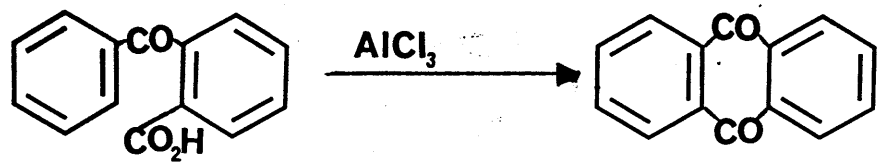
(3.5)

A number of analogous compounds have been prepared by this means and have found some use in industry.

The dye industry was one of the first to utilise the Friedel-Crafts synthesis and it is still of major importance in the industry. Anthraquinone dyes have nearly always been prepared from benzoyl benzoic acids, (equations 3.6, 3.7).

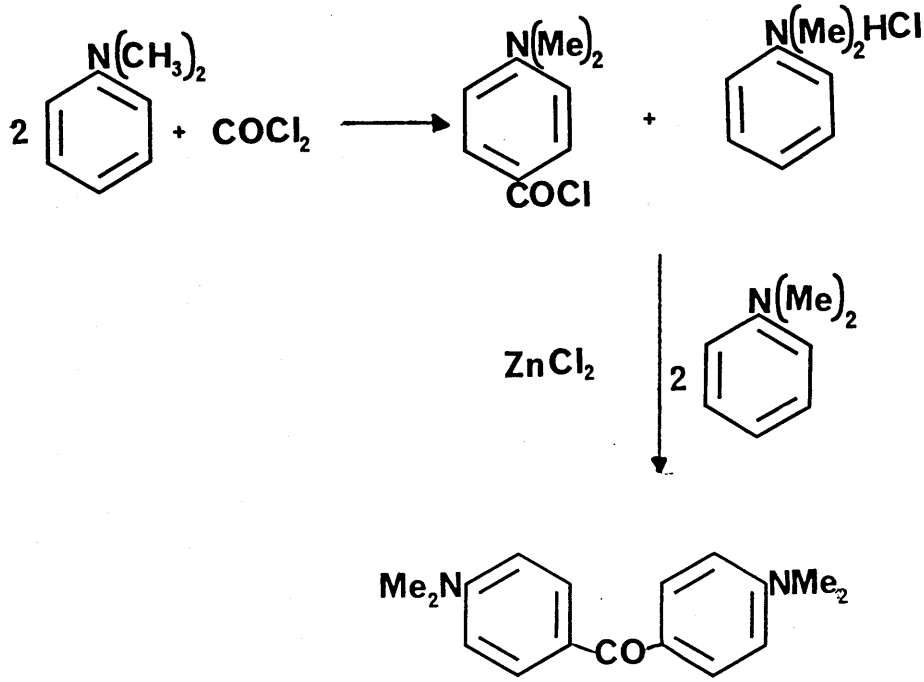


(3.6)



(3.7)

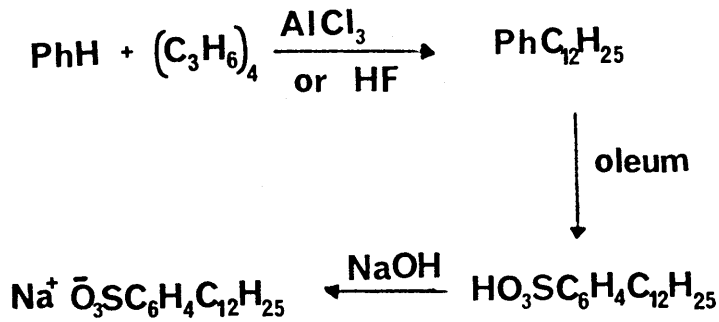
Michler's ketone, an important intermediate in the preparation of triphenylmethane dyes, is manufactured by the reaction of dimethylaniline with phosgene in the presence of zinc chloride, (equation 3.8).



(3.8)

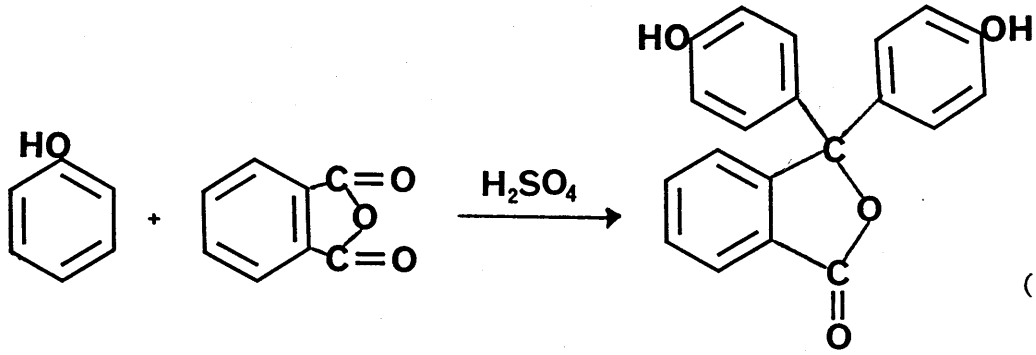
Indole and quinonoid dyes are also produced through Friedel-Crafts synthesis.

Alkyl arylsulphonates such as dodecylbenzene are used as detergents and manufactured by means of Friedel-Crafts synthesis, (equation 3.9).



(3.9)

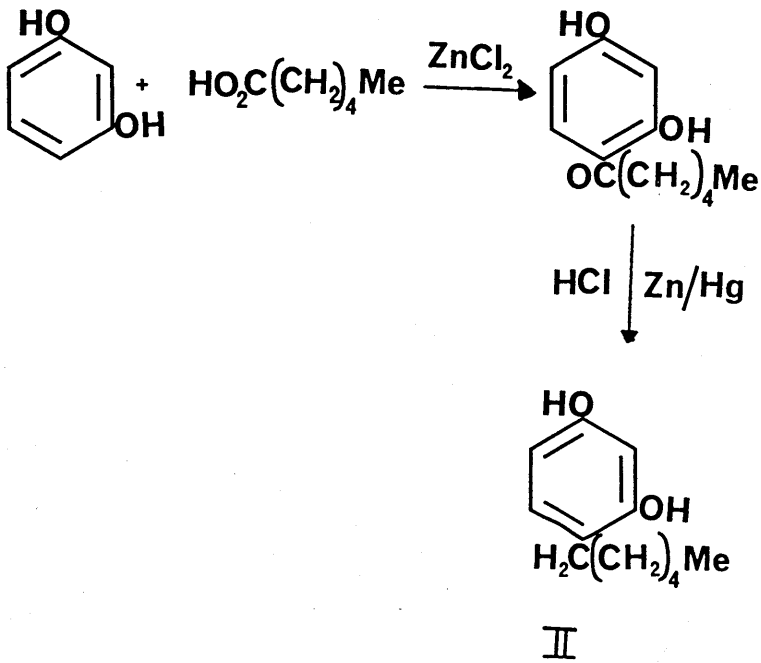
The pharmaceutical and cosmetics industry can afford numerous examples of Friedel-Crafts condensations, a few are included below (equations 3.10 - 3.13).



(3.10)

I

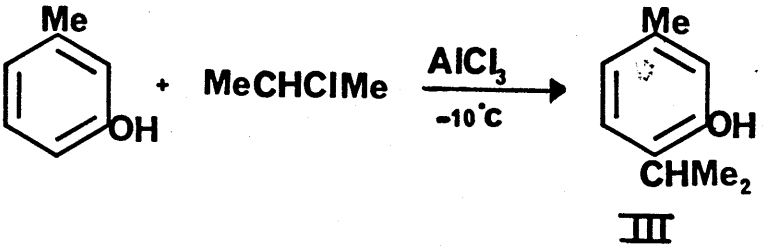
Phenolphthalein (I) is widely used as a laxative.



(3.11)

II

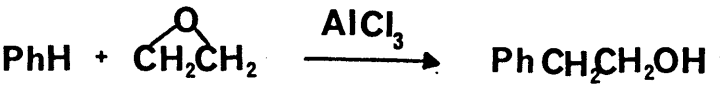
Doxylamine (II) is an antihistamine drug.



(3.12)

III

Thymol (III) is used as an antiseptic.



(3.13)

IV

β-phenylethyl alcohol (IV) is a constituent of artificial rose oil.

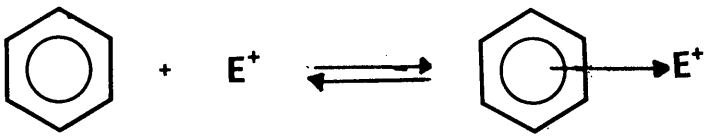
The future use of Friedel-Crafts type reaction in the chemical industry is very promising and with the arrival of new catalysts such as solid acids and super acids the number of applications can only increase.

4. Aromatic Electrophilic Substitution

Aromatic electrophilic substitution has been, and still is, one of the most intensively studied reactions in organic chemistry. Its general mechanism has now been fairly well established through the investigation of a number of reactions; namely nitration, sulphonation, halogenation and Friedel-Crafts alkylation and acylation.

4.1 - Mechanism

The reaction involves attack by an electrophile on an aromatic substrate such as benzene or one of its analogues, (equation 4.1).



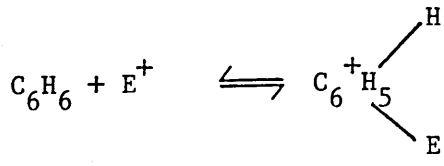
(4.1)

The electrophile can best be described as a reagent that accepts a pair of electrons and can be either a positive ion or a neutral molecule. Since the aromatic ring contains delocalised orbitals it can be reasonably assumed that the approaching electrophile E^+ may initially interact with the electrons. In fact, complexes of this type, referred to as π complexes, are known to exist. Toluene, for example, forms a 1:1 complex with hydrogen chloride at -78°C, the reaction being readily reversible.[22a] The possibility of bond formation can be disproved by the use of deuterium chloride. When hydrogen chloride is replaced with deuterium chloride in these systems, the aromatic compound produced on decomposition of the complex should contain deuterium if σ bonds are formed in the complex, but no deuterium has ever been found.[22a] Other evidence for the formation of a π complex comes from spectroscopy. There is very little change in the ultra-violet spectrum of the aromatic π complex indicating that there has been little disturbance of the π electron system. No colour change is observed and the solution is a non conductor of electricity. These observations suggest that the bonding involved in π complexes is of a very weak nature. With transition metals, aromatic species such as benzene can form stable compounds that involve the π-electrons in bonding. In many cases these compounds can be isolated and stored. Dibenzene chromium, for instance, can be isolated and forms dark brown crystals, although it is air sensitive. This is an example of a 'sandwich compound' or metallocene; the benzene ring forms a sandwich around the metal ion.

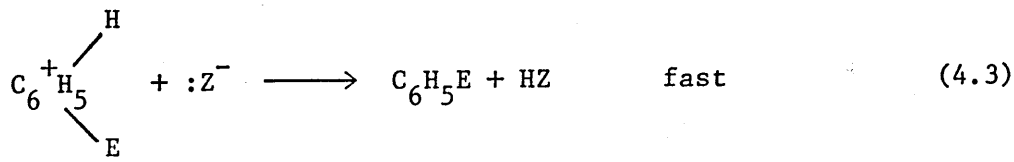
π complexes do, however, feature little in the traditional electrophilic substitution mechanism, since there is little evidence

which indicates that they are kinetically significant.

The mechanism itself essentially consists of two steps, (equation 4.2, 4.3).

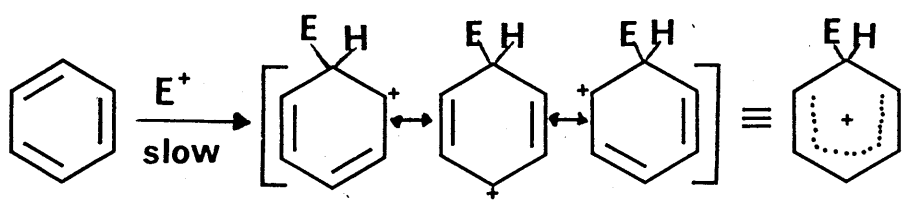


(4.2)



(4.3)

The first step involves electrophilic attack by the electrophile E^+ on the aromatic and is the rate limiting step; this results in E^+ becoming covalently bonded to the aromatic. Intermediates such as (II) are known as σ complexes, Wheland intermediates or arenium ions. Normally the σ complex is a highly reactive species due mainly to the loss of stabilisation from aromaticity, although some stabilisation is gained through resonance (equation 4.4).



(4.4)

II

As a result of this high instability, the σ complex reacts further. Two possible reaction paths are possible: 1) loss of E^+ or H^+ to give an aromatic compound or 2) addition, as in alkenes. Route (1) is the usual route as the stabilisation gained from reattaining the aromatic form is sufficient to prevent addition. If E^+ is lost then there is no overall reaction, whereas loss of H^+ results in electrophilic substitution.

There is strong evidence in support of this general mechanism. Isotope effects have been of major importance in establishing its validity. If a mechanism were possible in which the hydrogen ion left the benzene ring before the arrival of the electrophile or, if arrival and departure were simultaneous then the breaking of the carbon hydrogen bond would be involved in the rate limiting step. A substantial isotope effect would therefore be expected when comparing the rates of electrophilic substitutions in benzene and deuterobenzene; since breaking a carbon deuterium bond is energetically more demanding than breaking a carbon hydrogen bond. Experiments, however, show there to be either a small or zero isotope effect. This is as would be expected from the two step mechanism where the loss of hydrogen ion is not involved in the rate limiting step. Other evidence comes from the electrophilic substitution of aromatics by hydrogen ions, (equation 4.5).[22b]

$$ArMR_3 + H_3O^+ \longrightarrow ArH + R_3MOH_2^+ \qquad (4.5)$$

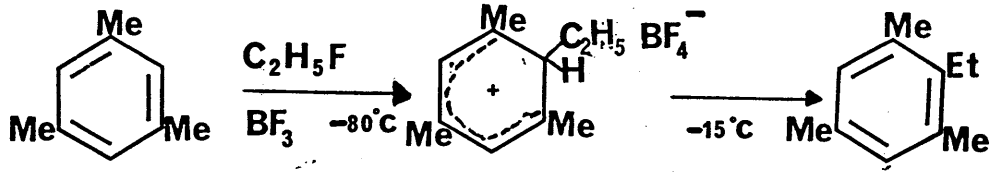
M = Si, Ge, Sn, Pb

R = Me, Et

Here the proton acts as the electrophile. Assuming that the

traditional mechanism is correct, (equations 4.2, 4.3), the use of D_3O^+ instead of H_3O^+ should result in a large isotope effect since the breaking of the oxygen deuterium bond is involved in the rate limiting step. These reactions do in fact exhibit a large isotope effect in a number of reaction systems lending further support to the mechanism.

The isolation and study of the σ complex has been possible,[23a] (equation 4.6).



(4.6)

The σ complex of mesitylene and ethyl flouride can be obtained at -80°C in the presence of boron trifluoride. Decomposition of this complex yields the normal substitution product. The properties of such σ - complexes are different to those of π complexes. σ complexes form coloured solutions that conduct electricity, showing the presence of positive and negative charges, and have a modified ultra violet spectrum. These isolated complexes provide extremely strong evidence in support of the mechanism. In addition to this nmr data has also been recorded for these complexes.[23b]

The fact that a σ complex is formed and aromaticity lost implies the expenditure of a considerable amount of energy, in other words, the activation energy for the process is high, (Figure 4.10.1).

One implication of this is a slow rate of reaction, but there are many aromatic electrophilic substitution reactions which are very fast. Two possible reasons for this could be: 1) energy is liberated by the complete formation of the new bond to the attacking electrophile and 2)

the σ complex is stabilised by delocalisation of the positive charge; this would result in the activation energy being smaller than expected.

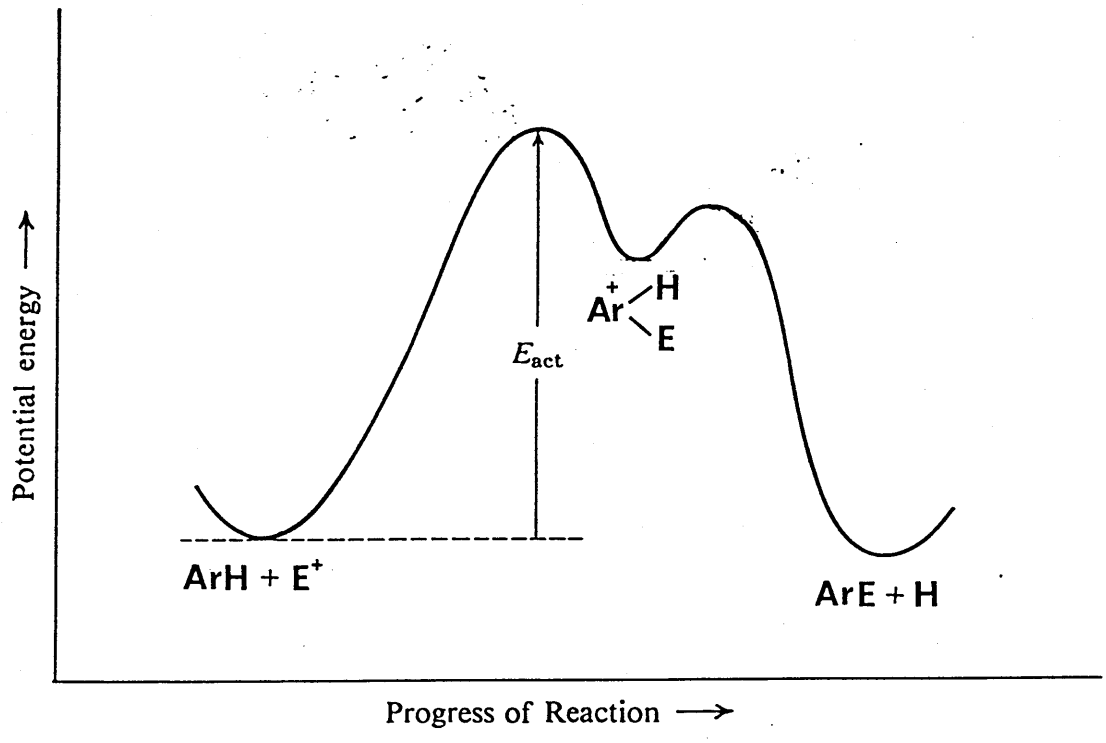
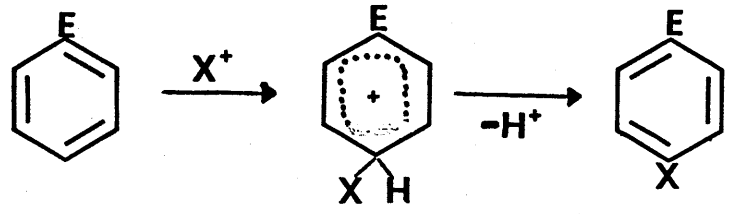


Fig. 4.10.1

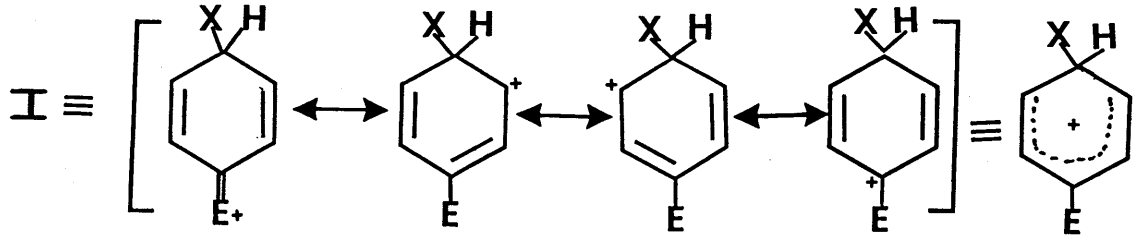
This diagram depicts the potential energy changes that occur during the course of electrophilic substitution reactions. The first step, which involves formation of the σ complex, is the slow step. The subsequent decomposition of the σ complex also involves an energy barrier, but the height of this is usually insignificant when compared to that of the first step.

The rate of aromatic electrophilic substitution is very susceptible to substituent effects. Electron donating groups such as Me, OMe, NH_2 and OH enhance the rate of substitution through inductive and resonance stabilisation. In such cases substitution normally takes place at the ortho and para positions, (equations 4.7, 4.8).



(4.7)

I



(4.8)

The same scheme can be drawn for ortho substitution, again showing inductive and resonance stabilisation of the intermediate by an electron donating group. In the case of electron withdrawing groups the situation is reversed. Groups such as NO_2, SO_3H, CO_2H, CHO, COR and CF_3 actually inhibit electrophilic substitution through both inductive and resonance effects. Sometimes substitution is not possible due to the strong deactivation; nitrobenzene, for example, cannot undergo Friedel-Crafts substitution. Where substitution does take place it is usually meta to the substituent.

These rules, however, are not always applicable. Instances can be found where the substituent has very little effect on the rate of reaction. Toluene is nitrated about twenty times faster than benzene in sulphuric acid, but the introduction of more methyl groups has very little effect on the rate of reaction. Xylenes and mesitylenes react only about twice as fast as toluene,[24] whereas in similar bromination reactions the rates are vastly enhanced by the introduction of more methyl groups. This phenomenon can be explained by looking at the reaction in terms of an encounter controlled mechanism. In the case of

nitration a position has been reached where the rate of reaction is limited by the rate of encounter between the electrophile, nitronium ions, and the aromatic substrate. Increasing the intrinsic reactivity of the aromatic does not increase the overall rate of reaction. In such circumstances every encounter leads to formation of product. These type of reactions are said to be diffusion controlled.

4.11 - Selectivity and Reactivity

It was mentioned earlier that electron donating substituents in a benzene ring activate the ring to further electrophilic substitution and that further substitution in these systems is predominantly ortho and para to the substituent. In a mono substituted benzene there are three possible positions for electrophilic attack, excluding ipso attack, and this in turn means three possible σ complexes, (Figure 4.10.2).

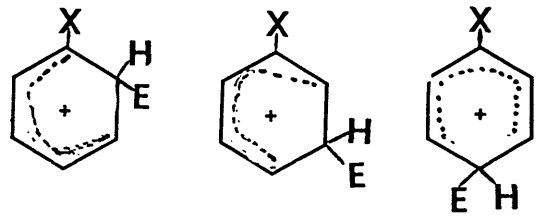


Figure 4.10.2 σ complexes for ortho, meta and para attack on C_6H_5X.

In the σ complexes the positive charge is concentrated predominantly at the positions ortho and para to the point of attack (equation 4.4). If electron donating substituents are present in these positions the σ complex is stabilised and the rate of reaction is accelerated. On the other hand, electron withdrawing groups in these positions have exactly the opposite effect and result in predominantly meta substitution.

The reactivity of any position in a substituted benzene relative to a position in benzene can be expressed in terms of a partial rate factor, p_f. For example, in the nitration of toluene the para position has a partial rate factor p_f, of 58. This means that the para position in toluene is nitrated 58 times faster than a corresponding position in benzene. The relative reactivities of two aromatic substrates such as benzene/toluene towards a common electrophile provides a measure of the intermolecular selectivity. Intramolecular selectivity, however, is determined by the relative reactivities of the ortho, para and meta positions in a substituted aromatic ring.

Normally the reactivity of a system is determined both by the activity of the aromatic substrate and the activity of the electrophile. Not all electrophiles are as reactive as one another. The nitronium ion not only attacks benzene and activated benzenes but also deactivated benzene rings such as nitrobenzene. Diazonium ions on the other hand, react only with rings containing strong activating groups such as hydroxy and amino groups. Empirically it is found that the greater the reactivity of the electrophile the smaller its selectivity, both inter and intramolecular, (Table 4.10.1).

Table 4.10.1 Relative rates and amount of meta and para substitution in electrophilic reactions of benzene and toluene.

	Relative Rate	Product Distribution; %	
Reaction	toluene/benzene	m	p
Bromination	605	0.3	67
Chlorination	350	0.5	40
Benzoylation	110	1.5	89
Nitration	23	2.8	34
Mercuration	7.9	9.5	69.5
Isopropylation	1.8	26	46

Intramolecular selectivity is normally measured with the aid of only the meta and para ratios since steric hindrance can interfere with the reactivity of the ortho position. Using a less reactive electrophile such as bromine para substitution will predominate and the electrophile will react preferentially with the more reactive substrate. With a very reactive electrophile such as isopropyl chloride, however, the converse is true; meta substitution increases and the electrophile only discriminates to a small extent between the two aromatic substrates.

This behaviour is explicable in terms of an early and late transition state. With a less reactive electrophile there is a late transition

state and this closely resembles the σ complex. Most of the charge in this case is centred around the ortho and para positions to attack, and therefore a para substituent can exert a large effect. Hence <u>para</u> substitution will predominate. In the case of a reactive electrophile the transition state comes much earlier and as a result less of the charge is borne by the ring. A <u>para</u> substituent will exert a smaller effect and this in turn will lead to a smaller difference between the <u>meta</u> and <u>para</u> positions.

By use of the Hammett equation intermolecular and intramolecular selectivity can be related mathematically (equations 4.9 and 4.10 respectively).[25]

$$\text{Log } f_p = \rho\, \sigma_p^+ \qquad (4.9)$$

$$\log (f_p/f_m) = \rho(\sigma_p^+ - \sigma_m^+) \qquad (4.10)$$

Manipulation of these two equations leads to the Brown 'selectivity relationship' (equation 4.11).

$$\log f_p = (\sigma_p^+/\sigma_p^+ - \sigma_m^+) \log (f_p/f_m) \qquad (4.11)$$

A plot of intramolecular selectivity against intermolecular selectivity for a series of electrophilic substitutions such as bromination, nitration and acetylation should therefore give a straight line of slope $\sigma_p^+/\sigma_p^+ - \sigma_m^+$. For a large number of reactions this is found to be

the case, but not all electrophilic substitutions obey this rule. Examples of these are discussed in the next section.

4.12 - π Complex Versus σ Complex

In the fifties Brown carried out an extensive study of the relationship between the relative rates of numerous electrophilic substitutions and the relative stabilities of the related σ complexes.[26] A simple linear relationship was observed as well as an adherence to the Brown Selectivity Relationship. Brown's conclusion from this was that the transition state for these reactions generally resembled a σ complex. Considerable evidence has now been accumulated in support of this proposition.

It was in 1961 that this view came under some criticism. In that year Olah and co-workers published the results of some nitration studies for which the Brown Selectivity Relationship broke down.[27] By the use of nitronium salts in sulpholan Olah found that the reactivity of toluene relative to that of benzene dropped to 1.7 or even less. Mesitylene was found to be only 2.7 times more reactive than benzene; whereas in chlorination it is thirty million times more reactive. In spite of this total loss of intermolecular selectivity, intramolecular selectivity was found to have been retained, the para:meta ratio being similar to that found in other nitrations. At first sight these results could not be explained in terms of the traditional electrophilic substitution mechanism.

To explain the results, Olah proposed that two intermediates were involved along the reaction pathway of electrophilic aromatic

substitution.[28] The first intermediate (IM1) resembles a π complex in nature, that is the nitronium ion is associated with the benzene, but not actually bonded to it. The corresponding transition state (TSI) was thought to resemble the starting aromatics (Figure 4.12.1). The second intermediate (IM2) was the σ complex in which the nitronium ion was actually covalently bonded to the benzene. The transition state associated with this (TSII) was similar to that in conventional nitration and as a result a normal isomer distribution was retained. Selectivities of π complexes do not vary greatly with increasing number of alkyl groups (Table 4.12.1). Where π complex formation is rate limiting the position of attack is not determined in the slow step. Therefore the p/m ratio would not be related to the rate of reaction and it is possible to have high positional selectivity but low substrate selectivity.

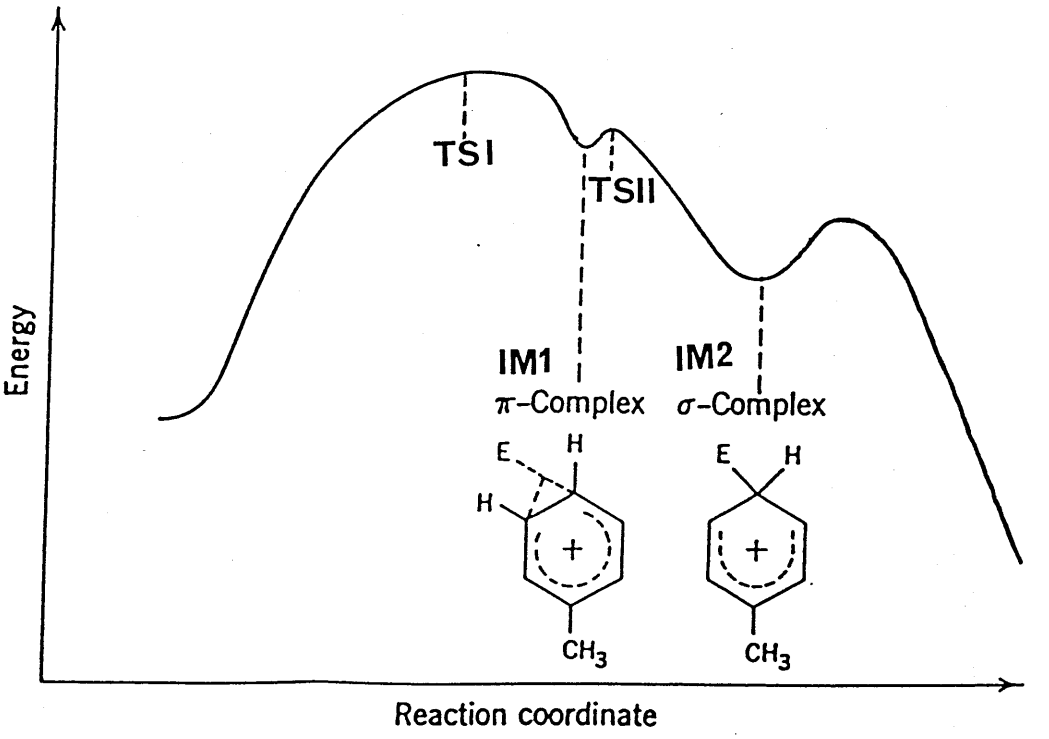


Fig. 4.12.1

π complexes are known to exist and there is plenty of evidence in their support (section 4.10), but the question that Olah's mechanism raises is whether they are kinetically significant. To test his proposal Olah correlated the results of his nitrations with the stability of the corresponding π complexes. Whilst the relative rates of nitration did indeed correlate with the π complex stability, the relationship was by no means perfect (Table 4.12.1).[28]

Table 4.12.1 Comparison of the relative rates of nitration of alkyl benzenes with π complex stabilities.

Substituent on benzene	π complex stability[29]	Relative rates[27] of nitration
none	1.00	1.00
Me	1.51	1.67
1,2 - Me_2	1.81	1.75
1,3 - Me_2	2.06	1.65
1,4 - Me_2	1.65	1.96
1,3,5 - Me_3	2.60	2.71

Olah's mechanism has aroused both interest and criticism.[30,31] The major part of the criticism centres around the practical technique employed by Olah in his measurements. Relative rates are normally measured by competition between two substrates competing for the same electrophile. The amount of electrophile is less than that necessary for complete reaction. This method, however, can only be employed if the rates of reaction is smaller than the rate of mixing. For Olah's

work some authors claim that this condition has not been met.[32]

It is believed that these nitrations are diffusion controlled reactions. Even so an encounter controlled reaction must have another intermediate prior to the formation of a σ complex. Otherwise the intramolecular selectivity would not be retained in these systems. At the moment this initial intermediate is usually referred to as an encounter-pair, but whether it is actually a π complex or not is still a matter of debate. Since this publication Olah has produced other evidence in support of his mechanism[33,34] and some of this will be discussed in section 5.

Before discussing the mechanism of Friedel-Crafts type reactions in detail, it is useful to review some typical examples of aromatic electrophilic substitutions.

4.13 - Nitration

Nitration has been the most intensively studied aromatic electrophilic substitution reaction to date. Numerous reviews of the subject are now available.[35] Several nitrating agents are now available and it is even possible to nitrate strongly deactivated aromatic substrates such as m-dinitrobenzene.

The early work was mainly concerned with nitrations using a mixture of sulphuric and nitric acids. Mechanistic studies on this system led to a scheme involving attack by a nitronium ion, (equations 4.13, 4.14).

$$2H_2SO_4 + HNO_3 \rightleftharpoons NO_2^+ + H_3O^+ + 2HSO_4^- \qquad (4.13)$$

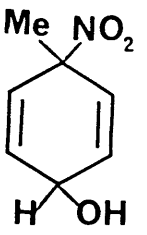
$$NO_2^+ + C_6H_6 \rightleftharpoons {}^+C_6H_5(NO_2)H \rightleftharpoons C_6H_5NO_2 \qquad (4.14)$$

($-H^+$)

Protonation of nitric acid by sulphuric acid leads to the formation of a nitronium ion. This has been confirmed by Raman Spectroscopy,[36] the nitronium ion giving a peak at $1400cm^{-1}$. Cryoscopic measurements on this mixture indicated the presence of four ions, lending further support to the mechanism.[37]

Other nitrating agents include, acetyl nitrate, nitronium salts, dinitrogen pentoxide and nitric acid itself. The essential feature of nearly all these nitrating agents is that the attacking species is the nitronium ion. Until recently all nitrations were thought to proceed via the traditional electophilic mechanism, but now it is obvious that there is more than the one classical mechanism for nitration.

Mechanisms involving ipso attack have received considerable attention over the last few years.[38] There is now strong evidence in support of the formation of ipso complexes. A number of such complexes, for example (III) have actually been prepared.[39]



III

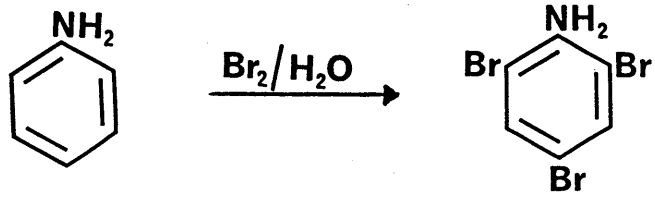
Ipso attack and substitution will be dealt with in section 4.16.

Another possible mechanism for nitration involves the formation of radical cation pairs.[40] This is usually believed to occur in encounter controlled nitrations (diffusion controlled).[41] Recently results have been obtained in support of this proposition.[42] Evidence for ^{15}N nuclear polarisation was found in the nitration of NN-dimethylanilines.[42] The phase of the nuclear polarisation in the amino and nitro groups from ipso attack, exchange, and rearrangement reactions was shown to be consistent with the partition of the radical pair $[ArN^{+}Me_2 \cdot NO_2 \cdot]$ between dissociation and combination. The esr spectrum was also consistent with the radical cation.[43a] The nitrous acid catalysed nitration of mesitylene gave marked ^{15}N nuclear polarisation attributed to the formation of a radical pair $[ArH^{+} \cdot NO_2 \cdot]$. However, direct nitration of mesitylene by the nitronium ion does not appear to involve this cation radical.[43b] Unlike mesitylene nuclear polarisation was observed both in the nitrous acid catalysed nitration and the nitronium ion nitration of durene again attributable to the radical pair $[ArH^{+} \cdot NO_2 \cdot]$.[43c] Similarly certain nitrations of p-nitrophenol are thought to involve the radical pair $ArO \cdot NO_2 \cdot$.[43d]

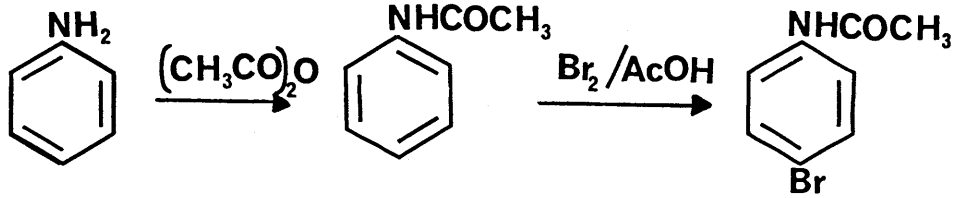
4.14 - Halogenation

Bromination and chlorination of aromatic substrates are usually carried out by the use of the free halogen in the presence of a catalyst, normally iron (III) chloride, iron, or other Lewis acids may be used. Certain reactive aromatic substrates such as phenols and anilines react without the need for a catalyst. Frequently polysubstitution can result (equation 4.15), although this can often be kept to a minimum

(equation 4.16).



(4.15)



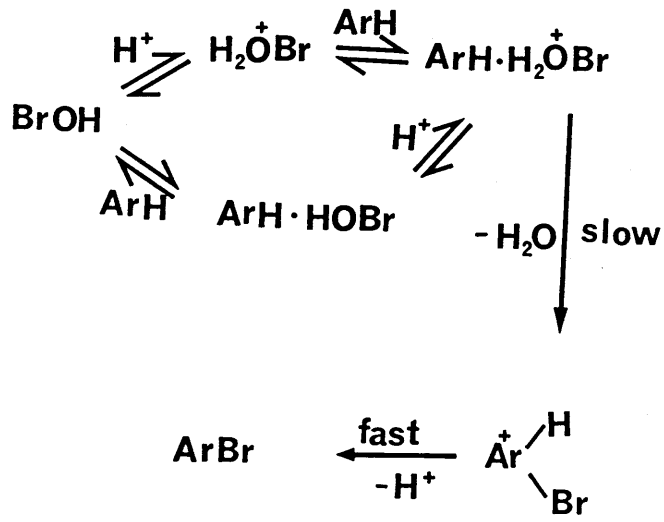
(4.16)

The mechanism of bromination and chlorination is similar to that of the conventional electrophilic aromatic substitution although some times additional steps are involved.

Certain bromination reactions carried out in the presence of nitromethane at 25°C using ferric chloride as a catalyst do not follow Browns Selectivity Relationship. Again the likelihood is that these are encounter controlled reactions. Examples of ipso attack are also available in halogenation reactions.[44]

The major problem involved with the study of bromination and chlorination reactions is the identification of the electrophile, that is whether it is X^+ or X_2. Chlorination in acetic acid has been proven to take place via Cl_2, as the rates of reaction are not affected by the addition of acids, bases, chloride or acetate ions. Reactions with 'positive chlorine' and 'positive bromine' do not, however, easily allow the identification of the electrophile. Bromine free hypobromous acid brominations are catalysed by acid, the electrophile being either

$BrOH_2^+$ or Br^+. Whilst in strongly acidic media this is probably true, in less acidic solutions it has been estimated that in order for the mechanism to agree with the experimental results the rates of reaction between the positive bromine and the substrate must be a million times faster than their rate of encounter. A mechanism for this behaviour has been suggested,[45] (equation 4.17).



(4.17)

The upper route is normally followed in strong acid media, whereas in weak acid media the lower route is applicable. Note that the rate determining step is the same for both pathways.

Direct fluorination using F_2 is not possible at room temperature although at lower temperatures it has been achieved.[46] Xenon difluoride and fluoroxytrifluoromethane have been used as fluoronating agents.[47,48] In some cases the reaction is thought to be electrophilic and in others free radicals are thought to be involved. The oldest method of introducing fluorine into an aromatic ring is via the Schiemann Reaction (equation 4.18).

$$ArNH_2 \xrightarrow[HCl]{HONO} ArN_2^+Cl \xrightarrow{NaBF_4} ArN_2^+BF_4^- \xrightarrow{heat} ArF \qquad (4.18)$$

Iodination can be accomplished by using free iodine in the presence of an oxidising agent such as HNO_3 or HIO_3. Alternatively ICl can be used. The true nature of the electrophile is not fully known, in some cases it is thought to be I^+ or I_3^+.[49]

4.15 - Sulphonation

Like nitration, sulphonation has been widely studied and several sulphonating agents are now available. However, unlike Friedel-Crafts alkylation, sulphonation of deactivated ring systems such as nitrobenzene and benzenesulphonic acid is possible. The reaction is usually carried out using sulphuric acid, but sulphur trioxide or chlorosulphonic acid may also be used.

Although the mechanism for sulphonation is fairly well established[50] problems still arise in the identification of the electrophile. This is mainly due to the large variety of species present in the solutions. Amongst these are H_2SO_4, $H_3SO_4^+$, $H_5SO_5^+$, HSO_4^-, H_3O^+, $H_5O_2^+$, SO_3, S_3O_9 and $H_2S_2O_7$. The reaction is also reversible and this can complicate matters further. Reversibility, however, can be reduced by employing a lower temperature for the reaction.[51]

It is now known that the nature of the electrophile changes with the concentration of acid, but in nearly all cases SO_3 is involved either

free or in combination with a carrier. With aqueous sulphuric acid of concentrations below 80% sulphonation correlates linearly with the activity of $H_3SO_4^+$; which can be thought of as a combination of H_3O^+ and SO_3. At concentrations above 85% a similar correlation is found with the activity of $H_2S_2O_7$, a combination of SO_3 and H_2SO_4. Of the two $H_2S_2O_7$ is the stronger electrophile, but a similar mechanism operates for both (equation 4.19).

$$ArH + SO_3X \underset{}{\overset{\text{fast}}{\rightleftharpoons}} Ar^{+}(H)(SO_3^-) \overset{\text{slow}}{\underset{\pm H}{\rightleftharpoons}} ArSO_2OH \qquad (4.19)$$

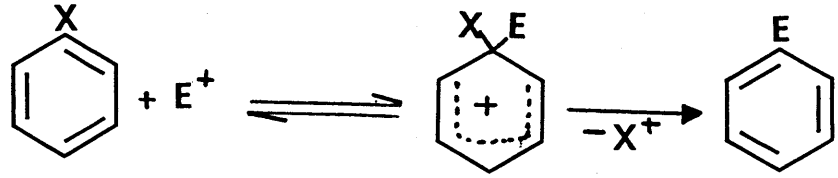
$$X = H_3O^+,\ H_2SO_4$$

Another important changeover occurs at 95% w/w sulphuric acid. Below this concentration of acid there is little or no deuterium isotope effect, but with higher concentrations an isotope effect can be observed. This suggests that proton loss in the second step becomes partially rate determining. An explanation of this can be obtained by considering the concentration of free base ions present. In lower acid concentrations the proton can be removed by the strong base HSO_4^-. With increasing acidity the concentration of this base falls rapidly leaving sulphuric acid as the only significant base present.

4.16 - Ipso Substitution

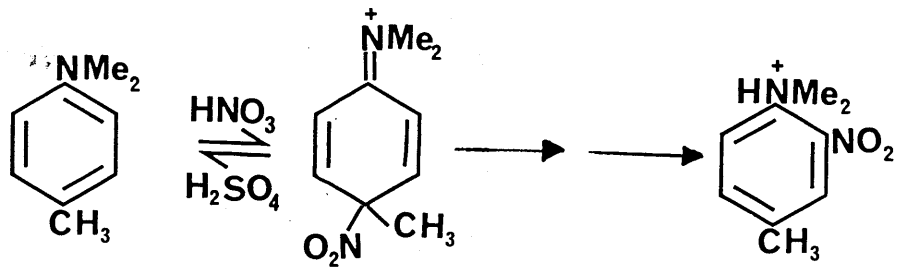
Until recently ipso substitution was a reaction that was frowned upon by most authors and as a result received little attention. Ipso substitution is concerned with electrophilic attack on the substituted

carbon atom, the ipso position. If the substituent group is a suitable leaving group then it can be displaced by the attacking electrophile, (equation 4.20).



(4.20)

Since the early seventies evidence has continued to grow in support of electrophilic substitutions involving initial ipso attack. The decomposition of an ipso intermediate can take a number of routes. Firstly as mentioned above direct ipso substitution can occur (equation 4.20). Alternatively the starting material can be regenerated. Another, and more important, possible path is a 1,2 or 1,3 shift of the electrophile to produce the ortho or meta substituted compound via a second intermediate, (equation 4.21).[52a]



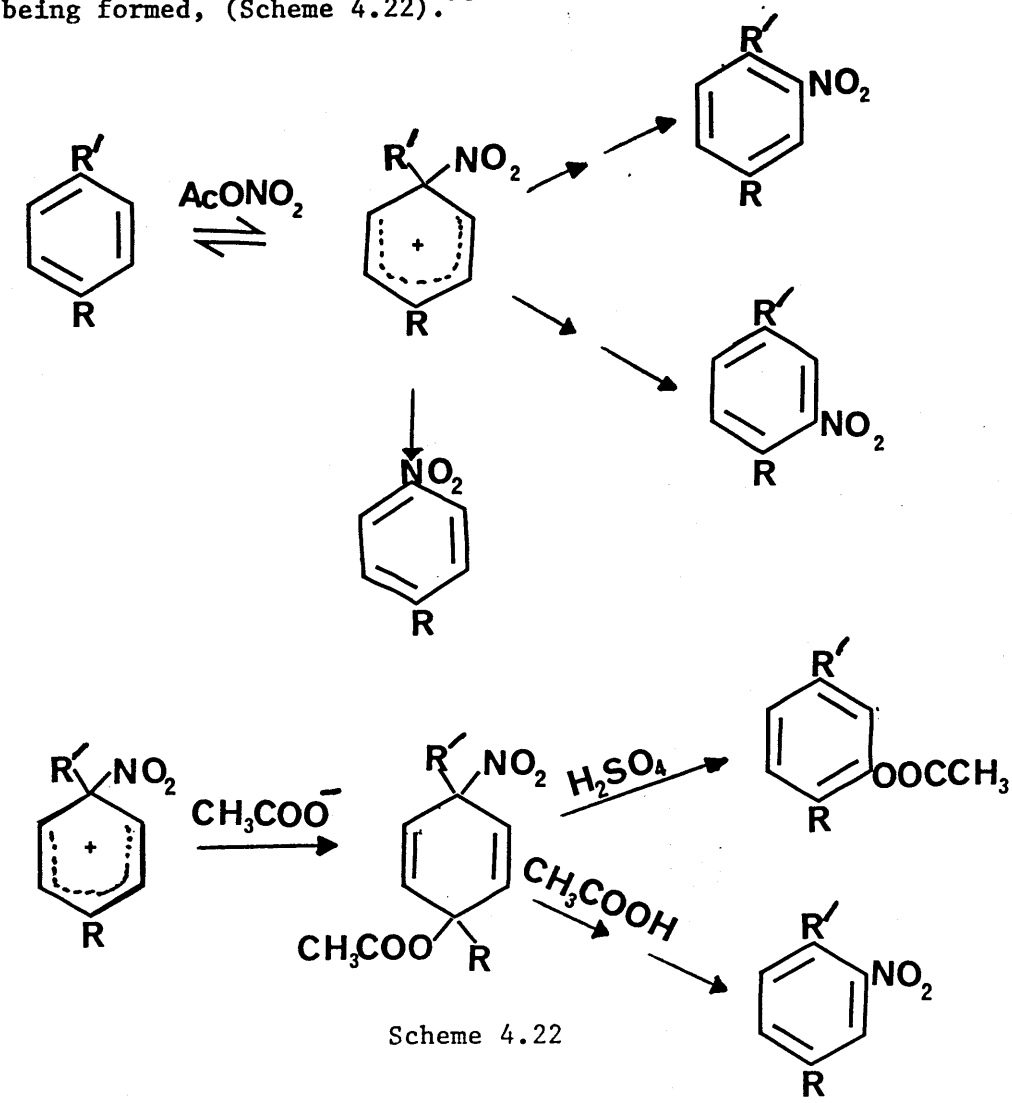
(4.21)

ipso intermediate

In this example, the ipso intermediate has been studied by means of both ^{1}H and ^{13}C NMR spectroscopy.[52b] Such 1,3 shifts have also been observed in the nitration of 4-nitrophenol.[52c]

Finally the ipso intermediate can react further and undergo nucleophilic attack to give a cyclohexadiene derivative. The reaction of p-cymene with acetyl nitrate at 0°C results in a number of products

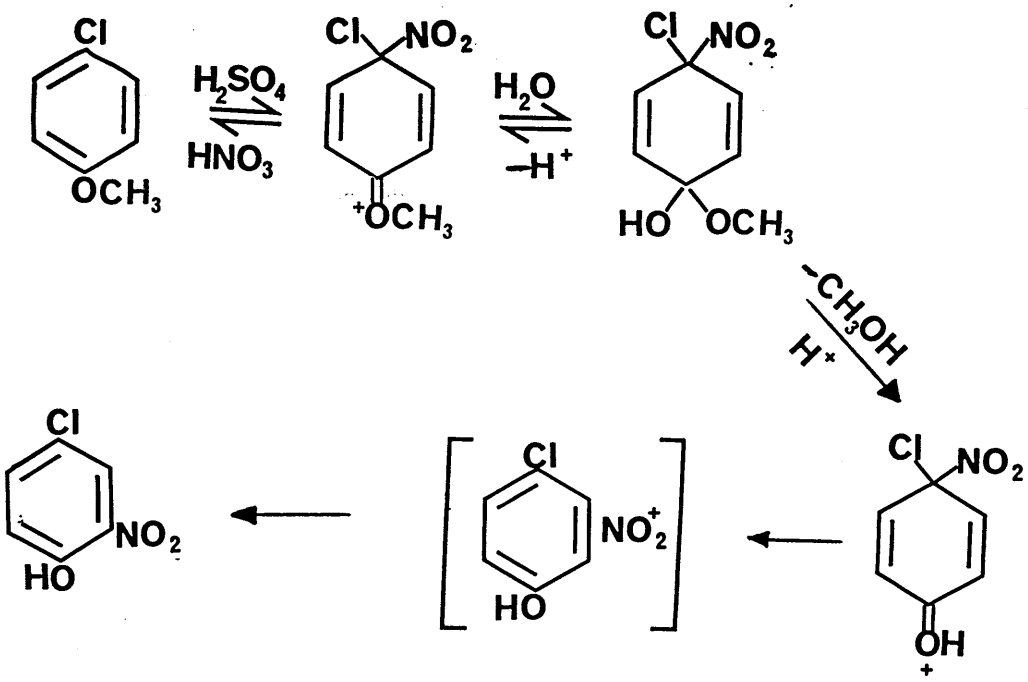
being formed, (Scheme 4.22).[53]



Scheme 4.22

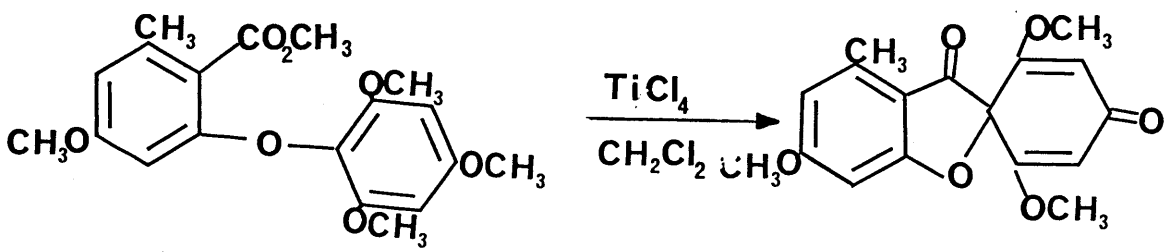
When certain anisoles are nitrated the product is often the corresponding phenol derivative rather that an anisole. For example the nitration of 4-chloroanisole with a sulphuric and nitric acid mixture gives some 4-chloro-2-nitro phenol, scheme 4.23.

Using ^{18}O labelling it was found that the phenolic group comes from the solvent. By using ^{18}O labelled 4-chloroanisole it was found that the resulting phenol had no ^{18}O, hence the formulation of an ipso adduct mechanism.[54]



Scheme 4.23

Evidence for ipso intermediates has also been obtained in other electrophilic substitutions. In Friedel-Crafts chemistry an intramolecular acylation has been observed producing an ipso substituted product, (equation 4.24).[55]



(4.24)

The o-phenoxybenzoic ester would readily give an acylium ion presumably complexed with the Lewis acid, by an $A_{AC}1$ type mechanism because of the steric acceleration and stabilisation of the positive charge produced

by the adjacent electron donating substituents.

5. The Mechanism of Friedel-Crafts Type Reactions

Mechanistic studies of the Friedel-Crafts reaction have proved to be very difficult due mainly to the occurrence of precipitation in many of the reactions. This coupled with isomerisation, reversibility, dealkylation and polyalkylation make this one of the most difficult electrophilic aromatic substitution reactions to investigate. In spite of these problems a substantial amount of research has been carried out and consequently the general features of the mechanism have been established. Some controversy, however, still remains as to the possibility of π complex formation in the rate limiting step. The role of the catalyst and solvent has also been investigated.

5.1 - The Role of the Catalyst and Solvent

In the early days of Friedel-Crafts chemistry it was thought that the catalytic behaviour of Lewis acids was somewhat different to that of the Bronstead acids. Subsequently it has been shown that in many cases Lewis acids require a co-catalyst in order for reaction to take place. This co-catalyst, sometimes referred to as a 'proton donor', is normally water. One of the reasons why Friedel-Crafts reactions proceed so smoothly is because the aluminium trichloride used always contained water or hydrogen chloride. It is very difficult to get true anhydrous aluminium chloride. The real catalysts in these reactions is therefore probably of the form $AlCl_3OH^- H^+$ or $H^+ AlCl_4^-$. Nowadays the two types of catalysts are thought to be very similar in their action.

The catalytic activity of aluminium chloride is superior to that of sulphuric acid. If a proton acid is involved in both cases why should this be so? A measurement of the acidity of the two systems should provide an answer. The Hammett Acidity Function, H_o has been measured for the system of hydrogen fluoride plus 7% weight boron trifluoride and has been found to be -16.6.[56] This compares with -11 for 100% sulphuric acid indicating that the former is much stronger acid by a factor of about 10^5. Aluminium trichloride systems are believed to have a similar acidity and therefore greater catalytic activity than sulphuric acid and similar catalysts.

Solvent effects have been studied and it is now clear that the choice of a correct solvent results in not only higher yields, but can also reduce the catalyst : reagent ratio. Often the solvent employed, in Friedel-Crafts reactions, is one of the reactants. In alkylation reactions, however, this is usually not possible due to polyalkylation and therefore an inert solvent has to be employed. Hydrocarbons in general are poor solvents for the acidic halide catalyst, whereas systems containing donor atoms such as alcohols, ethers, nitriles, acids, and nitro compounds are usually good solvents for these catalysts.

The choice of a solvent can have a major effect on the course of a reaction. In carbon disulfide acetylation of naphthalene yields mainly 1-acetyl naphthalene. If the solvent is changed to nitrobenzene, however, 2-acetyl naphthalene becomes the major product. In this case it is thought that the aluminium chloride/acetyl chloride form a complex with nitrobenzene resulting in a very bulky electrophile, such that β-substitution becomes pronounced as a result of steric hindrance.

5.2 - Mechanism of Alkylation

Despite the problems encountered in alkylations such as precipitation, reversibility and dealkylation an understanding of the general mechanism has been established.

It was discovered that for a number of alkylations the rate was dependent on not only the concentrations of substrate and electrophile, but also on the concentration of the catalyst, (equation 5.1)

$$\text{Rate} = k\,[\text{ArH}][\text{RCl}][\text{catalyst}] \qquad (5.1)$$

ArH = Aromatic substrate

RCl = Alkyl Halide

A mechanism consistent with this rate equation is outlined below (equation 5.2).

$$\text{RCl} + \text{AlCl}_3 \rightleftharpoons (\text{RCl:AlCl}_3) \underset{\text{slow}}{\overset{\text{ArH}}{\rightleftharpoons}} \text{Ar}\overset{+}{\underset{\text{R}}{\overset{\text{H}}{\diagup\diagdown}}} \text{AlCl}_4^- \underset{\text{fast}}{\rightleftharpoons} \text{ArR} + \text{HCl} + \text{AlCl}_3 \qquad (5.2)$$

The second step of the mechanism is rate determining which is in agreement with the conventional mechanism. As to the nature of the electrophile this has not been fully established. Evidence to date suggests that the electrophile can range from a free carbonium ion to a loose molecular complex.

$R^+ + AlCl_4^-$	$R^+AlCl_4^-$	$R\text{-}Cl\text{-}AlCl_3$	$RCl \cdot AlCl_3$
free carbonium ion	ion pair	co-ordinated complex	loose molecular complex

The structure of the electrophile is thought to be dependent on not only the nature of R but also on both the solvent and catalyst. Formation of the free carbonium ion is unlikely as this would be very reactive and result in step 1 becoming rate determining. In this case the concentration of the aromatic substrate would not appear in the rate equation.

It is well known that alkyl halides react with Lewis acids (such as $AlBr_3$) to form 1:1 complexes: A solid 1:1 complex of methyl bromide and aluminium bromide has been isolated at -78°C. These complexes have been found to be weakly conducting and slow halogen exchange is also observed. It is possible that when R is able to form a relatively stable carbonium ion, for instance if R is t-butyl then the free carbonium ion may be the electrophile. Certainly in such a case, a loose molecular complex would be unlikely. Low inter and intramolecular selectivity is a feature of Friedel-Crafts alkylations, this indicates the involvement of highly reactive electrophiles. An inference from this is that the electrophile has a very polar nature and may in certain circumstances even be an ion pair. Further evidence for this comes from the observations of Wagner-Meerwein type rearrangements of the electrophile in a number of reactions (equation 5.3).

$$ArH + CH_3CH_2CH_2Br \xrightarrow{AlCl_3} ArCH(CH_3)_2 + HBr \qquad (5.3)$$

Isolation of intermediates has been possible in a number of instances and these lead to the conclusion that σ complexes are involved in the mechanism. This has already been discussed in Section 4.

5.21 - Rearrangement, Reversibility and Dealkylation

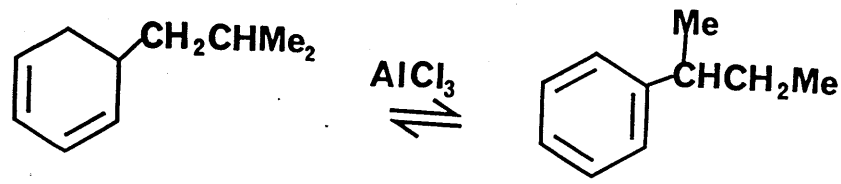
Often Friedel-Crafts alkylations result in the product having a rearranged alkyl group, (equation 5.4).

$$C_6H_6 + Me_3CCH_2Cl \xrightarrow{AlCl_3} Ph\text{-}\overset{\overset{Me}{|}}{\underset{\underset{Me}{|}}{C}}\text{-}CH_2Me + HCl \qquad (5.4)$$

This is explicable on the basis that the polarised complex between the Lewis acid and alkyl halide is polar enough for rearrangement to take place. The resulting complex is what would be expected if carbonium ions were involved, a tertiary species formed in preference to a secondary which in turn is preferred to a primary. If a milder catalyst (for example, ferric chloride) is employed then no rearrangement takes place. The implicatior of this being that the complex is now not polarised enough for rearrangement.

The actual proportions of products obtained, however, does not always reflect the relative stabilities of the carbonium ions. In other words attack on the aromatic species by the first formed complex may be

faster than its rearrangement. The study of these rearrangements is further complicated by the fact that Lewis acids can not only rearrange the alkyl halide, but also the alkylated product, (equation 5.5).



(5.5)

Aluminium chloride can not only be used to introduce alkyl groups into aromatics, but is also able to remove them from alkyl aromatics. This is known as dealkylation. As a result of this feature of Lewis acid chemistry it is usually said that Friedel-Crafts alkylations are reversible. The reaction, however, does not display true reversibility in the liquid phase, for if that were so then an alkyl benzene should give as products benzene and an alkylating agent. Treatment of ethylbenzene with aluminium chloride produces benzene and polyethylbenzenes; although benzene can be distilled off rapidly from this system no ethylene can be found, furthermore the residue is highly ethylated. This is because at liquid phase temperatures the thermodynamic equilibrium lies well over to the side of alkylation. In gas phase work, however, there is an indication of true equilibrium, as a small amount of the olefin is produced at temperatures of about 500°C.

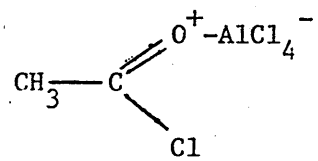
5.3 - Mechanism for Friedel-Crafts Acylation

Essentially the same mechanism and rate law apply to acylation as to alkylation. It is, however, found that in a number of acylation reactions where the rate relationships are first order in substrate and

acyl chloride, the order with respect to the catalyst is variable.

The nature of the electrophile in acylation studies is better understood than in alkylation. This does not mean, however, that there is only one electrophilic structure involved. Both an acylium ion or a polarised complex are possible for the electrophile and which obtains depends upon the conditions.

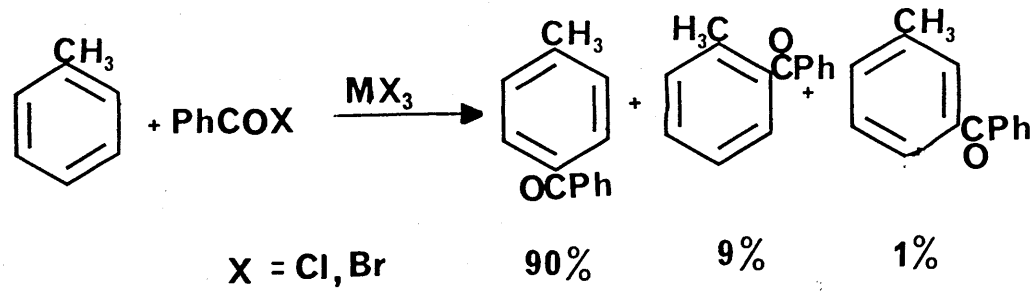
Free acetylium ions have been detected by infra red studies in acetyl chloride and aluminium trichloride mixtures. The existence of 1:1 and 1:2 complexes has also been demonstrated. Further evidence for the existence of a free acetylium ion has come from x-ray studies. These show that the 1:1 complex is coordinated via the oxygen, as shown below.[57]



Structure of a 1:1 complex between aluminium trichloride and acetyl chloride.

The 1:2 complex probably involves complexation with chlorine.

In the benzoylation of toluene with benzoyl chloride or benzoyl bromide the same proportions of products are obtained, regardless of the Lewis acid used, (equation 5.6).



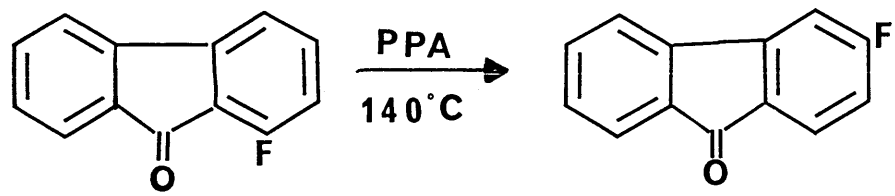
X = Cl, Br 90% 9% 1%

(5.6)

An inference from this is that the same electrophile is involved in both cases, namely $PhCO^+$. In many other instances, however, there is virtually no ortho product formed; this indicates a much bulkier electrophile, possibly a polarised complex. This leads to a variable rate dependence on the concentration of the catalyst. The rate limiting step of nearly all acylations is believed to be the formation of a σ complex, as in other conventional electrophilic aromatic substitutions.

5.31- Acylation Reversibility

Until recently there had been little evidence for reversibility in acylations; certainly no rearrangement of the acyl group has ever been observed. In 1977 a paper was published and reported the rearrangement of an aromatic fluoro ketone in the presence of polyphosphoric acid,[58] (equation 5.7).



(5.7)

Recently Gore et al have studied the reversible acetyl exchange of acetyl mesitylene in the presence of aluminium trichloride[59] and protiodeacylation of mono and di-acylmesitylenes in 90% sulphuric acid.[59b] Although such work provided evidence for reversibility in acylation, this does not imply that it is as widespread as in alkylation. Not every acylated aromatic is capable of reversibility. It is thought that reversibility is only possible for ketones, with bulky neighbouring substituents, whose acyl groups are tilted

out-of-plane with respect to the aromatic nucleus such that they loose some resonance stabilisation.

5.4 - σ complex versus π complex in Friedel-Crafts Reactions

Some aspects of the controversy concerning the role of π complexes in electrophilic aromatic substitution have already been dealt with in Section 4. In addition to the work cited there, Olah has published a number of papers relating to Friedel-Crafts chemistry, which he claims show quite clearly the involvement of π complexes.

In the first of these Olah described the reactions between toluene, benzene and a number of substituted benzyl chlorides.[60,61] By altering the substituent he was able to vary the electrophilicity of the electrophile. The results of these reactions are shown below in Table 5.1.

The most electrophilic reagent employed in this work was p-nitro benzylchloride, which had a low inter molecular selectivity (K_t/K_b = 2.5). Being the most reactive reagent it would be expected to be the least selective both intermolecularly and intramolecularly. Olah suggests that in this case the transition state resembles a π complex rather than a σ complex. With p-methoxy benzylchloride the situation is reversed. The electrophile here is the least reactive, with stabilisation of the electrophile being due to the methoxy group, and therefore the most selective. As a result the transition state resembles a σ complex. Olah's argument thus suggests that the position of the transition state is variable, with very reactive electrophiles going via a transition state resembling a π complex and less reactive

electrophiles proceeding through a σ type transitions state.

Table 5.1 $TiCl_4$ catalysed benzylations of benzene and toluene with various benzyl chlorides at 30°C.

		methyldiphenyl methane isomer (%)		
$XC_6H_4CH_2Cl$	Kt/Kb	Ortho	Meta	Para
p-NO_2	2.5	59.6	6.2	34.2
o-F	4.8	39.3	7.8	52.9
p-F	8.7	43.0	6.5	50.5
o-Cl	4.6	38.8	7.2	54.0
p-Cl	6.2	40.1	5.0	54.9
H	6.3	40.5	4.3	55.2
o-CH_3	19.1	24.6	3.4	72.0
p-CH_3	29.0	31.4	2.1	66.5
o-CH_3	60.3	23.2	1.3	75.5
p-CH_3O	97.0	28.6	1.5	69.9

To substantiate his findings Olah published further work, based on acylation and benzoylations.[62] Acetylation studies of toluene and benzene were carried out using acetyl chloride and acetyl fluoride using $AlCl_3$ and BF_3 as the catalyst respectively, (equation 5.8).

$$ArH + RCOX \xrightarrow{MX_3} ArCOR + HX \qquad (5.8)$$

Ar = C_6H_5, $CH_3C_6H_4$

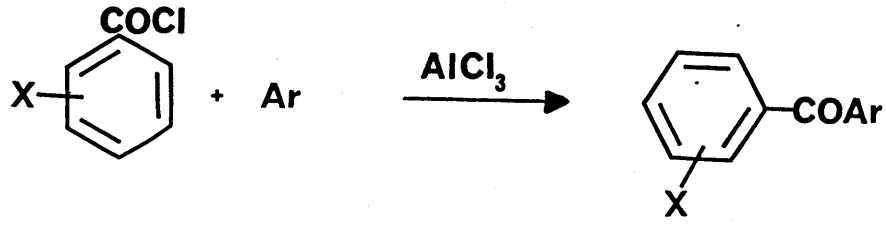
R = H, CH_3, C_2H_5, i-C_3H_7 , CH_2Cl, CH_2Cl_2

X = Cl, F

In both cases high inter and intra molecular selectivity was observed, signifying a σ type transition state. The $K_t:K_b$ ratios were 141 and 130 and p-substitution was predominant (over 95%).

Using formyl fluoride, however, a different picture emerged. The $K_t:K_b$ ratio was reduced to 34.6 and para substitution amounted to only 53.2% with over 43% ortho isomer. Olah suggested that the formylating agent is far more electrophilic in nature than in the case of acetyl fluoride. The stronger electrophile makes less demand on the aromatic substrate in the transition state resulting in an earlier transition state, which resembles a π complex rather than a σ complex.

Following a suggestion that such effects were a result of steric hindrance, Olah studied the acylations using a range of substituted acetyl chlorides. The results obtained correlated best with the electrophilicity of the reagent rather than the steric size. For example, dichloro acetyl chloride gave over 97% ortho product, whereas acetyl chloride produced only 2.5%. The former electrophile is the bulkier of the two and on steric grounds should have yielded less than 2.5% ortho isomer. Olah also studied the benzoylation of toluene and benzene with substituted benzoyl chlorides in the presence of aluminium trichloride catalyst. The results of this study are presented below (equation 5.9 and Table 5.2).



(5.9)

Ar = C_6H_6 or $CH_3C_6H_5$

Table 5.2 Relative rates and isomer distributions in the benzoylation of toluene and benzene with substituted benzoyl chlorides in nitromethane at 25°C.

X	K_t/K_b	% Ortho	% Meta	% Para
1,2,3,4,5-$(F)_5$	16.1	35.4	7.8	56.8
2,4-$(NO_2)_2$	29.0	42.4	3.0	54.6
P-NO_2	52	9.5	1.2	89.3
2,5-$(F)_2$	96.2	12.3	1.6	86.1
H	153.5	8.1	1.2	90.7
P-CH_3	164.4	7.8	1.1	91.1
P-F	170	8.0	1.1	90.9
2,4,6-$(CH_3)_3$	196	2.3	0.6	97.1
P-OMe	233	14.9	1.5	83.6

By varying the substituent X on the benzoyl chloride it was possible to vary the electrophilicity of the reagent. The tabulated results are in

agreement with earlier findings. The most reactive electrophile is pentafluoro benzoyl chloride and as a result it is the least selective, both inter and intramolecularly. Whereas, with reagents at the bottom of the table, the weaker electrophiles, the situation is reversed. Again Olah offers an explanation in terms of a variable transition state.

The conclusions reached by Olah have been criticized by Decoret et al[63] who undertook a theoretical study of the role of the solvation energy in competitive Friedel-Crafts reactions. From their calculations they conclude that the results obtained by Olah are explicable in terms of solvation. They stipulate that solvated benzyl cation electron affinities are reversed compared to the naked cation electron affinity order. Thus, solvation reverses the cation electron affinity order and in the transition state the smaller the induced cation stabilisation energy the greater the cation positive charge. It should also be noted that for a given electrophile the K_t/K_b ratio decreases with increasing catalyst and solvent concentrations.

Criticism has also been forthcoming concerning the consistency of the results obtained from competitive and non-competitive kinetic data. DeHaan et al[64] have recently reported that in excess aromatic, benzylation proved to be exceedingly difficult to run in a homogeneous reproducable fashion. The results depended strongly upon the amount of moisture present. With 0.0006% wt. water there was almost immediate precipitation in half the benzene runs and in all but one toluene run. A more accurate determination of the inter and intramolecular selectivities for benzyl chloride alone indicates that all transition states resemble σ complexes.

Much of Olah's evidence for the presence of π complex formation derives from the breakdown of the Brown Selectivity Relationship. This breakdown seemed to occur even when mixing was not a problem. DeHaan has recently carried out a thorough study of Friedel-Crafts type reactions which were earlier reported as exceptions to this Selectivity Relationship. He used vacuum line techniques to overcome the problem of moisture. DeHaan found that most of the reactions did indeed fit the selectivity relationship suggesting that the transition state of the rate determining step does resemble a σ complex. This was proven to be true for benzylations in excess aromatic,[64b] acylation,[64c] sulfonylation,[64c] formylation with 1,1-dichloromethyl methyl ether,[64d] isopropylation,[64e] benzylation with p-nitrobenzylchloride in nitromethane [64f] and tert-butylation in nitromethane.[64g] Most of these reactions had previously suffered from contamination with moisture such that the reaction profiles were curved and the zero time rate was difficult to determine.

5.5 - Gas Phase Friedel-Crafts Reactions

Recently a good deal of interest has been aroused in the study of gas phase Friedel-Crafts reactions. Gas phase work has enabled the study of reactions of carbocations free from counter ion pairing and solvent effects.

The properties of carbocations in the gas phase are somewhat different to those in solution. For instance $^{+}CH_2X$ (X=F, Cl, Br) reacts with benzene in the gas phase to give methyl benzenes and halomethylbenzenes.[65] Alkyl cations can also interact with n-donor substituents on an aromatic nucleus. Isopropyl cations react with

phenol to give an ether and ring substituted compounds.[66] Tert-butyl cations behave similarly.[67] For this reaction, under kinetic control and at high pressures the ether:phenol ratio is 8 in the presence of ammonia and the ortho:para ratio for the substituted phenol is 0.4. At lower pressure where thermodynamic control operates the two ratios are reduced to 0.25 and 0.04 respectively. These results can be explained in terms of an initial kinetically favoured attack on the oxygen followed by isomerization of the protonated product and then subsequent rearrangement to the more thermodynamically stable product.

Further evidence in agreement with this explanation is available both in solution and gas phase work. In solution chemistry the reaction of CT_3^+ with halobenzenes seems to involve some interaction with the halogen giving methyl phenyl halonium ions which rearrange to give ring substituted compounds. Returning to the gas phase, the isopropylation of chlorobenzene with isopropyl cation produces 89.6% of the ortho isomer,[68] with toluene, however, only 46% ortho isomer is obtained. This provides clear evidence that chlorine n-electrons must be involved in the orientation of electrophilic attack.

Before going on to review cyclodehydration reactions it is useful to examine acidity function theory.

6. Acidity Functions

The pH scale is a useful measure of the acidity of a system but only at high dilutions. Solutions having a pH below 1.5 are much more acidic in nature than would be assumed from their pH. For instance 10^{-2}M sulphuric acid has the same pH as pure sulphuric acid, although the

latter is a much stronger acid. So it seems logical to devise a new scale which will reflect the true acidity of a system. Many such scales are now available and are grouped under the general heading 'Acidity Functions'. Extensive research has been carried out in the field of acidity functions and many reviews of the subject can be found in the literature.[69-73] Consequently only a brief treatment of the theory relevant to this work will be given here.

When a base B is protonated an equilibrium can be written for the protonated form (equation 6.1). The equilibrium constant (K) for this reaction is given by equation (6.2) and from this the pKa can be defined as it is simply the negative logarithm of K.

$$BH^+ \overset{K}{\rightleftharpoons} B + H^+ \qquad (6.1)$$

$$K = a_B.a_{H^+}/a_{BH^+}; \qquad a = \text{activity} = \text{conc. x activity coeff. (f)} \qquad (6.2)$$

$$pKa = -\log K = \log(a_{BH^+}/a_B a_{H^+}) = \log(a_{BH^+}/a_B) - \log a_{H^+} \qquad (6.3)$$

For dilute solutions the pKa can be written using first the concentrations as the activity coefficients will be unity, (equation 6.4).

$$pKa = \log [BH^+]/[B] + pH = \log I + pH \qquad (6.4)$$

$$\text{where } I = [BH^+]/[B]$$

The pKa for dilute solutions is easily obtained from equation (6.4), but for concentrated acids the activity coefficients of the species

must be taken into account as pH is not a valid concept for concentrated acids.

A new scale was therefore advanced by Hammett and given the symbol H_o.[74] The H_o acidity function is given by equation (6.5) and is valid for ideal Hammett bases such as primary aromatic amines.

$$pKa = H_o + \log I \qquad (6.5)$$

Here H_o has replaced the pH in equation (6.4) and is itself defined by equation (6.6)

$$H_o = -\log(a_{H^+} f_B / f_{BH^+}) \qquad (6.6)$$

H_o reduces to pH for dilute solutions where the activity coefficients are unity.

H_o is measured by the use of series of chemically similar indicators. The most basic of these, A, is used to calculate the pKa for dilute solutions where $[HA^+]/[A]$ is easily measurable by spectroscopic techniques. When this ratio becomes too large (>10) another less basic indicator, B, has to be employed. Now $[HB^+]/[B]$ is measured for a solution where H_o is known, this allows the calculation of the new pK_B. Once this indicator becomes obsolete another less basic indicator, C, is employed and so on until the full acidity scale has been determined. The assumption inherent in this approach is that the ratio of the activity coefficients is the same for all indicators used. Hence the need to use chemically similar indicators. It is not surprising therefore that a plot of H_o against LogI does not always have a slope of exactly 1; slopes of $1 \pm .1$ are usually taken as meaning that the

indicator is following H_o.

Other acidity functions can be defined similarly using indicators other than primary aromatic amines, for example H_A[75] is defined using amides. Other functions are defined using various carbonyl compounds,[76-78] heterocycles[79,80] and pyridine N-oxides.[81,82]

One important acidity function is defined for protonation-dehydration processes and is called H_R,[83] (equations 6.7, 6.8).

$$Ar_3COH + H^+ \overset{K_r}{\rightleftharpoons} Ar_3C^+ + H_2O \qquad (6.7)$$

$$H_R = pK_r - \log I \qquad (6.8)$$

H_R is usually measured by means of triarylcarbinol indicators. A diagram depicting the various different acidity functions for sulphuric acid is shown in fig. 6.1.

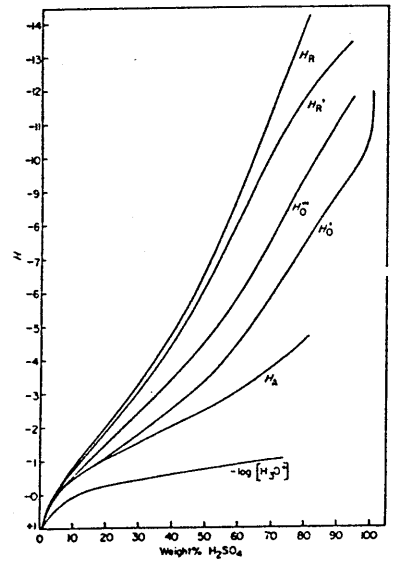


Fig. 6.1 - Various acidity functions for sulphuric acid/water mixtures

With so many acidity functions now available it would be useful if a function could be derived that could replace these with just one acidity function. A number of attempts have been made to achieve this goal. The main stumbling block to achieving this lies with the ratio of the activity coefficients f_B/f_{BH^+} (where B is the organic base indicator used to define the acidity function). In most cases this ratio is taken to be constant for the series of organic bases used in deriving the acidity function. However, it is far from constant and considerable variation is seen from one functional group to another. With substituent changes on the functional group smaller discrepancies are found. So a new system to replace the acidity functions would have to take into account these variations.

One of the first treatments to combat these problems was put forward by Bunnett and Olsen.[84] They used the H_o acidity function which is defined in equation (6.6) which can be rearranged to give equation (6.9).

$$H_o = -\log[H^+] - \log f_{H^+} f_B / f_{BH^+} \qquad (6.9)$$

They then went on to point out that the activity coefficient ratio of one base will be linearly related to another (x) rather than being constant, (equation 6.10).

$$\log f_{H^+} f_X / f_{XH^+} = (1-\phi) \log f_{H^+} f_B / f_{BH^+} \qquad (6.10)$$

Equations (6.9) and (6.10) can be combined and rearranged to give

equation (6.11).

$$\log f_{H^+}f_X/f_{XH^+} = -(1-\phi)(H_o + \log[H^+]) \qquad (6.11)$$

The pKa of a base is defined by equation 6.3, for the base x it is given by equation (6.12).

$$pKa = -\log K_a = -\log[H^+][X]/[XH^+] - \log f_{H^+}f_X/f_{XH^+} \qquad (6.12)$$

When equation 6.12 is combined with equation 6.11, equation (6.13) can be obtained.

$$\log[X]/[XH^+] = H_o - \phi(H_o + \log[H^+]) - pKa \qquad (6.13)$$

When this is looked at in conjunction with equation (6.5) a clear resemblance can be seen in that equation (6.13) defines a new acidity function $H_o - \phi(H_o + \log[H^+])$. The quantities ϕ (slope) and pKa (intercept) can be found by plotting $\log I + H_o$ against $H_o + \log[H^+]$. This method has proved quite popular as it gives good results both for acidic and basic media.[73]

Another more recent treatment was outlined by Marziano, Cimino and Passerini.[85] This method is known by these names and it is also called the Cox and Yates method.[86,87] Other names for it are (i) excess acidity method and (ii) x-function method.

For an indicator base B equation (6.5) can be rearranged to equation

(6.14).

$$\log I - \log[H^+] = \log f_B f_{H^+}/f_{BH^+} + pKa \qquad (6.14)$$

Now in this method the excess acidity X was defined in terms of an anchor reference base B^* and this is given by equation (6.15).

$$X = \log f_{H^+} f_{B^*}/f_{B^*H^+} \qquad (6.15)$$

It was then stated that the activity coefficient ratio of a base B will be related to X by equation (6.16).

$$\log f_{H^+} f_B/f_{BH^+} = m^* X \qquad (6.16)$$

If equation (6.16) is substituted into equation (6.14) equation (6.17) is obtained.

$$\log I = \log [H^+] + m^* X + pKa \qquad (6.17)$$

Here the new acidity function is $\log[H^+] + m^*X$. Values for X can be easily obtained from existing ionization ratio data.[88,89] This method although different from the Bunnett and Olsen method gives basically the same results, the pka is the same and $m^* = 1 - \emptyset$.[90a]

The merits of the Excess acidity method have recently been questioned by Johnson.[90b] He employed physicochemical relationships to compare

the pKa values derived from the Hammett acidity function method and the Excess acidity function method. The estimates of the pKa values derived from the Hammett acidity function method were found to approximate, in many cases, more nearly to the correct thermodynamic quantities than those derived from the Excess acidity method.

6.1 - The use of acidity functions in mechanistic studies

Over the last forty years acidity function data has been widely used in the study of acid catalysed reaction mechanisms. Hammett was the first to show that a linear correlation existed between the rate of reaction and H_o.[74] For a number of reactions it was found that a plot of log k (rate constant) against H_o gave a straight line of unit slope. These reactions were of the type shown in equation (6.18) where the decomposition of SH^+ to products did not involve a molecule of water.

$$S + H^+ \rightleftharpoons SH^+ \longrightarrow \text{product} \qquad (6.18)$$

In reactions where a molecule of water was involved a plot of log k against $\log[H^+]$ was found to give the best results, (equation 6.19). This became known as the Zucker-Hammett hypothesis.[91]

$$S + H^+ \rightleftharpoons SH^+ \xrightarrow{H_2O} \text{product} \qquad (6.19)$$

With the advent of new acidity functions, such as H_A, H_R, etc., it emerged that reactions earlier thought to follow $\log[H^+]$ did in fact

correlate better with these new acidity functions. In other words, changes in the substrate often required the use of acidity functions other than H_o. As a result of these inaccuracies the Zucker-Hammett hypothesis is no longer used.

Acidity functions do however, provide us with a useful guide to the structure of the transition state. Where this resembles the protonated form a linear correlation will be observed between log k and H_x, the slope being unity. With slopes other than unity the transition state will probably be somewhat different to the protonated form. The protonation of a substrate S is given by equation (6.20) and on application of the transition state theory equation (6.21) is obtained.

$$S + H^+ \xrightarrow{k_{obs}} SH^+ \qquad (6.20)$$

$$S + H^+ \underset{}{\overset{K}{\rightleftharpoons}} {}^{\neq}SH^+ \xrightarrow{k'} SH^+ \qquad (6.21)$$

$$\text{rate} = k'[{}^{\neq}SH^+]$$

As the equilibrium constant $K = ([{}^{\neq}SH^+]/[S][H^+])(f\,{}^{\neq}SH^+/f_S f_{H^+})$

$$\text{rate} = k'K[S][H^+].f_S f_{H^+}/f\,{}^{\neq}SH^+ \qquad (6.22)$$

For the pseudo first order reaction shown in equation (6.20)

$$\text{rate} = k_{obs}\,[S] \tag{6.23}$$

By substituting equation (6.22) into (6.23) equation (6.24) is obtained.

$$k_{obs} = k'K[H^+].f_S f_{H^+}/f\,{}^{\neq}_{SH^+} \tag{6.24}$$

Taking logarithms and rearranging gives

$$\log k_{obs} = \log(a_{H^+} f_S / f_{SH^+}) + \log(f_{SH^+}/f\,{}^{\neq}_{SH^+}) + \log k'K$$

By definition $H_X = -\log(a_{H^+} f_B / f_{BH^+})$

$$\text{therefore, } \log k_{obs} = -H_X + \log(f_{SH^+}/f\,{}^{\neq}_{SH^+}) + \log k'K \tag{6.25}$$

Now supposing that the transition state (${}^{\neq}_{SH^+}$) is product-like (SH^+) then $f{}^{\neq}_{SH^+} = f_{SH^+}$ and therefore equation (6.25) can be written as

$$\log k_{obs} = -H_X + \log k'K \tag{6.25a}$$

It can be seen from this that plot of log k_{obs} against H_x should give a

straight line of unit slope. For a transition state which is reactant-like $f^{\neq}_{SH^+} = f_S f_{H^+}$ and in this case equation (6.24) reduces to

$$\log k_{obs} = \log [H^+] + \log k'K$$

Therefore for a reactant-like transition state a plot of log k_{obs} against log$[H^+]$ should be a straight line of unit slope.

For reactions in which protonation is followed by the loss of water the H_R acidity function must be used, (equation 6.26).

$$ROH + H^+ \rightleftharpoons R^+OH_2 \rightleftharpoons R^+ + H_2O \longrightarrow \text{Products} \qquad (6.26)$$

In systems where the transition state is R^+-like a plot of log k_{obs} against H_R shoud give a straight line of unit slope.

The use of these acidity functions can be exemplified by a number of reactions one of which is the decarboxylation of triphenyl acetic acid in acid media. Dittmar[92] studied this reaction and found that a plot of log k_{obs} against H_o resulted in a slope of 2.6. This was reinvestigated by Elliot and Hammick[93] and the result was confirmed. Because of this high slope it was believed that diprotonation of triphenylacetic acid was involved even though there was only one basic centre in the molecule. In light of these findings a mechanism for the decarboxylation process was put forward,[93] (equation 6.27).

$$Ph_3CCO_2H + H^+ \rightleftharpoons Ph_3CCO_2H_2^+$$

$$Ph_3CCO_2H_2^+ + H_2SO_4 \xrightarrow{\text{slow}} PhC^+ + CO + H_3O^+ + HSO_4^- \qquad (6.27)$$

Here the protonated species interacts with the acid solvent without proton transfer taking place. This was clearly not a satisfactory conclusion. Deno and Taft re-examined the reaction and plotted log k against H_R, the resulting slope was found to be 0.99.[94] Clearly then the reaction was following H_R rather than H_o and in light of this a new mechanism was suggested. The rate limiting step in this case was the loss of CO, (equation 6.28 and 6.29).

$$Ph_3CCO_2H + H^+ \rightleftharpoons H_2O + Ph_3C\text{-}CO^+ \qquad (6.28)$$

$$Ph_3C\text{-}CO^+ \xrightarrow{\text{slow}} Ph_3C^+ + CO \qquad (6.29)$$

Other examples of use of these acidity functions will be given in section 7.

Although the use of acidity functions to provide mechanisms is potentially a powerful technique a number of discrepancies can be found. This is perhaps not surprising in view of the inherent assumptions made about the activity coefficients. One way of overcoming these assumption problems is to use Bunnett and Olsens's

acidity function which was defined in equation (6.13), instead of H_o. Substituting this acidity function into equation (6.25a) gives equation (6.30).

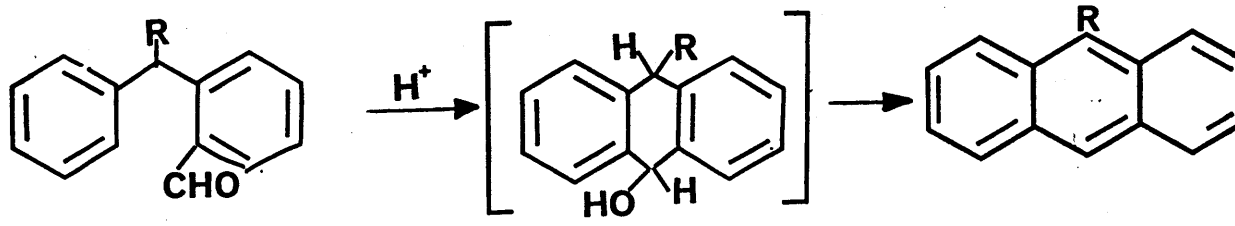
$$\log k_{obs} + H_o = \emptyset(H_o + \log[H^+]) + \text{const.} \qquad (6.30)$$

Here a plot of $\log k_{obs} + H_o$ against $(H_o + \log[H^+])$ gives a line of slope $\emptyset$. If a negative value for $\emptyset$ is obtained it indicates that water is not involved in the rate limiting step.[95] If however, a value in excess of +0.22 is obtained the involvement of water is indicated. This method has now been applied to a very large number of reactions and the results obtained prove to be more reliable than with earlier methods.

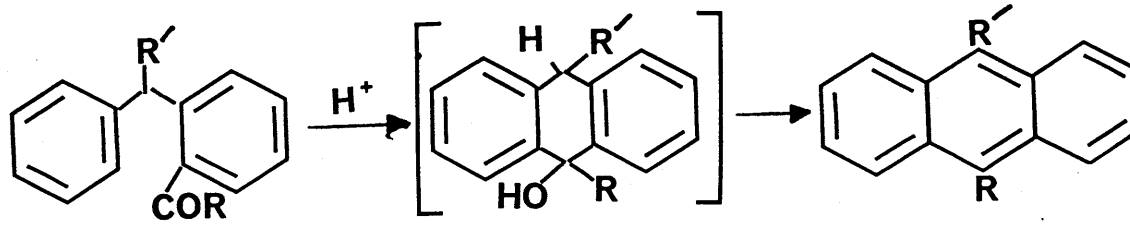
7. Cyclodehydrations

Cyclodehydration is simply a reaction in which intramolecular cyclisation takes place with the loss of water. A number of reagents are available to effect this reaction and virtually all of them are Friedel-Crafts catalysts. Sulphuric acid is probably the most widely used of these. The compounds usually cyclised are acids, alcohols, aldehydes and ketones. Normally a cyclisation results in either a six or five membered ring although larger rings are possible.

Anthracene derivatives can be prepared by the use of aromatic ketones and aldehydes (equations 7.1, 7.2).

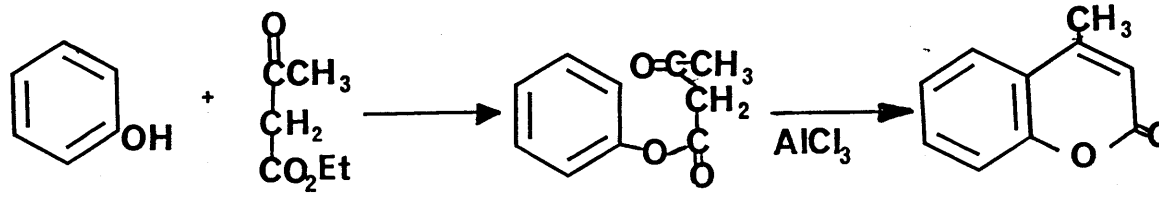


(7.1)



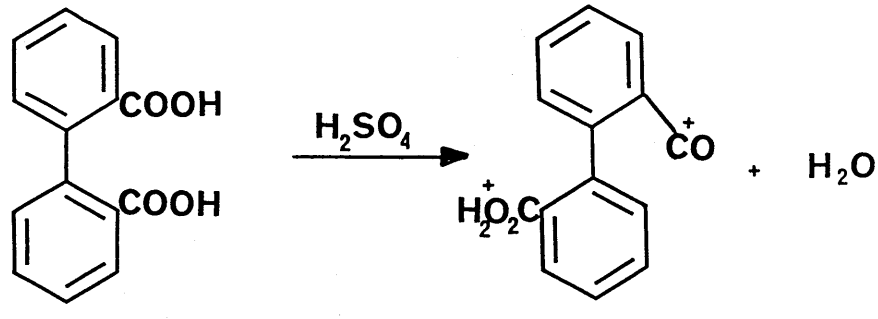
(7.2)

Coumarins can be prepared by the condensation of phenols and -keto esters, (equation 7.3).



(7.3)

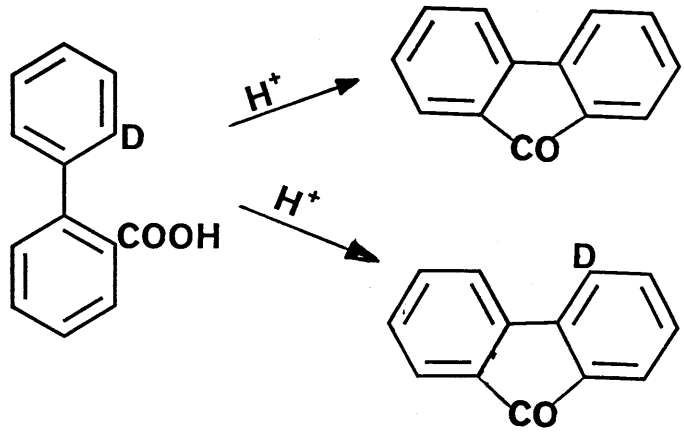
The Friedel-Crafts cyclodehydration of a number of acids have been extensively studied. Mechanistic studies on the cyclodehydration of 2,2'-diphenic acid show that the acid is completely protonated in 99% sulphuric acid, above this acidity water is lost from the molecule to give a carboxonium ion, (equation 7.4).[96]



(7.4)

Reaction rates follow the H_o acidity function indicating that it is the

protonated acid that acts as the electrophile. With the introduction of 5 and 5' substituents it was found that electron releasing groups accelerated the reaction, whilst electron withdrawing groups retarded it. By assuming that the electronic effects of an ortho substituent were similar to those of a para substituent a relationship was sought between the log of the rate constant and σp^+ constants. A good linear correlation was found with a large negative slope, indicative of an electrophilic substitution reaction. The implication of this is that the conventional electrophilic substitution mechanism is operating in this type of system. A study of the kinetic isotope effects, however, gave some unexpected results. 2-Deutero-2'-carboxybiphenyl was cyclised in sulphuric acid and the reaction products analysed,[97] (equation 7.5).

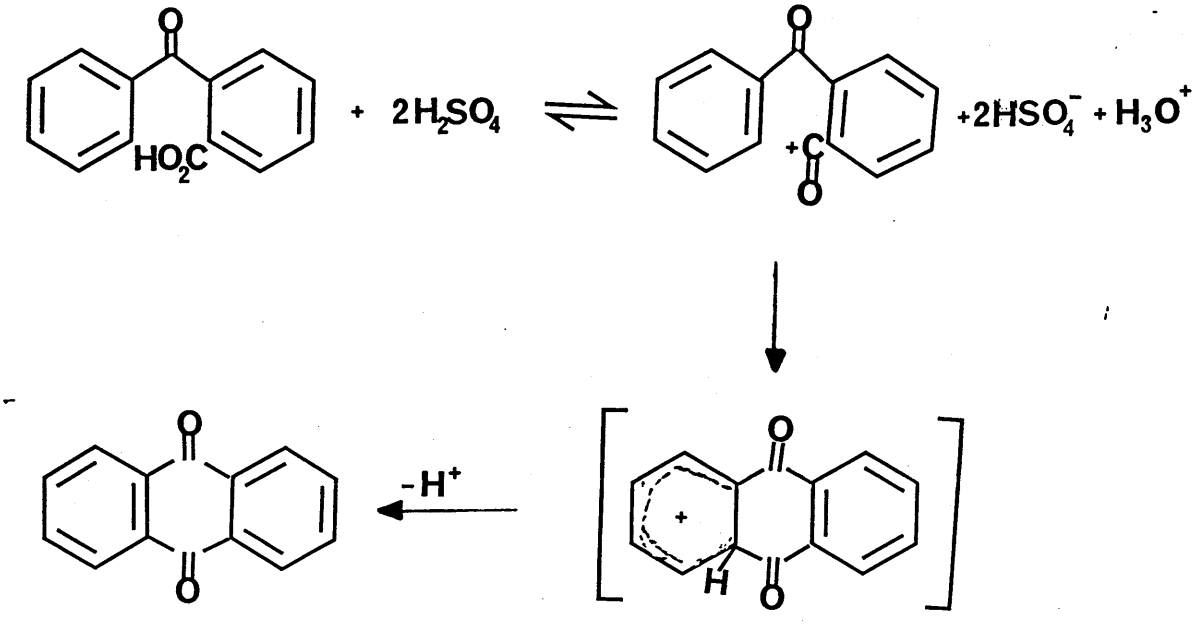


(7.5)

This analysis showed a definite isotope effect with k_H/k_D = 1.31. It is clear from this that hydrogen loss in this system is partially rate determining. A possible explanation for this is that the formation of a σ complex is disfavoured by geometrical restrictions, in other words a planar transition state and product are not geometrically favourable.

The Friedel-Crafts cyclisation of 2-benzoylbenzoic acid is probably the best known cyclodehydration reaction and therefore the reaction which

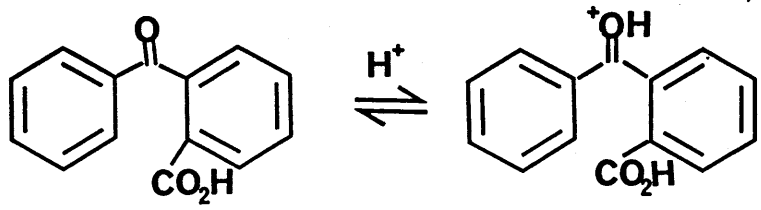
has been the most extensively investigated.[98] Hammett and Deyrup noted in 1932 that the reaction follows the Ho acidity function. It was not until 1957, however, that Long and Paul pointed out that this correlation was not a very good one; the reaction, they said, should correlate better with H_R.[99] This modification was in accord with the mechanism suggested by Newman in 1942,[100] (equation 7.6).



(7.6)

That four ions are formed in the initial step has been confirmed by cryoscopic measurements. In 1959[98] Vinnik stated that at low acidities the protonated acid predominates, and that only at high acidity does ionisation take place to any great extent to give the carboxonium ion. Their results, however, confirmed that cyclisation was the rate determining step.

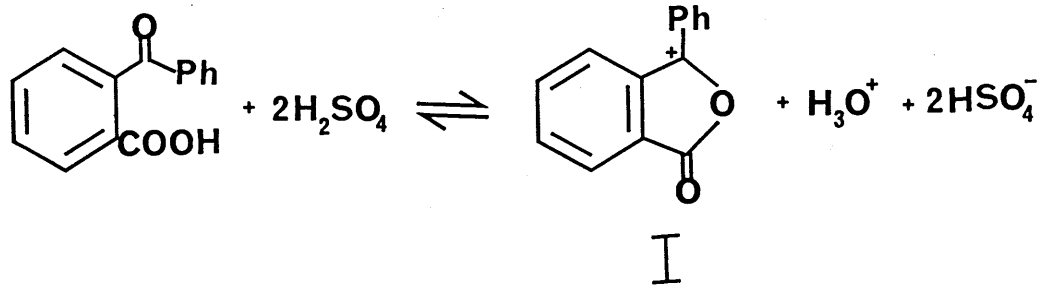
Recently Noyce and Kittle[98,101a] carried out a thorough investigation into the mechanism of this reaction, their results have cast some doubts on the excepted mechanism. They pointed out that initial protonation will occur on the keto oxygen, (equation 7.7).



(7.7)

Evidence for this comes from an investigation of substituent effects in the benzoyl ring. The introduction of a methoxy group in the 3-position of the benzoyl ring considerably enhances the basicity of the molecule. This strongly supports initial protonation on the keto oxygen. Protonation studies of acids and ketones have generally shown ketones to be more basic than acids. For instance benzoic acid is protonated in 81.5% sulphuric acid which corresponds to a H_o value of -7.58. Benzophenone on the other hand is protonated at a H_o value of only -6.39.

The protonation of benzoylbenzoic acid was studied in concentrations of sulphuric acid in the range 90-100%. At these concentrations benzoylbenzoic acid undergoes complete ionisation, (equation 7.8).



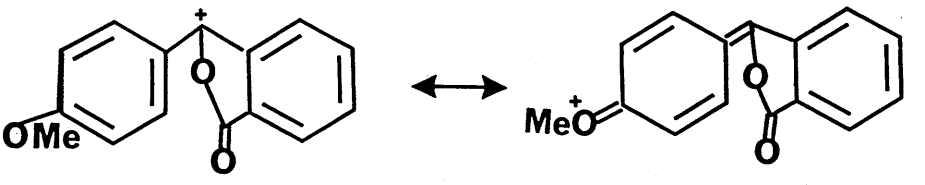
I

(7.8)

That the dominant species in solution is I and not the free carboxonium ion was proved by pouring a solution of I in 100% acid into methanol. The resultant products were a mixture of normal and pseudo esters.

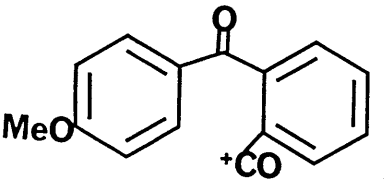
The introduction of electron donating groups into the 4 or 4' position, that is <u>para</u> to the keto group, results in the lactol carbonium ions being formed at substantially lower sulphuric acid concentrations.

With electron donating substituents in the 3-position of the benzoyl ring an enhanced rate of cyclisation was observed. However, when the same substituents were placed in the 4-position of the benzoyl ring the reaction rate was found to be substantially lower than that of the benzoylbenzoic acid itself. By examining the structure of the 4-substituted lactol carbonium ion (II) it can be seen that here the substituent is in a position where it can stabilize this carbonium ion through resonance.



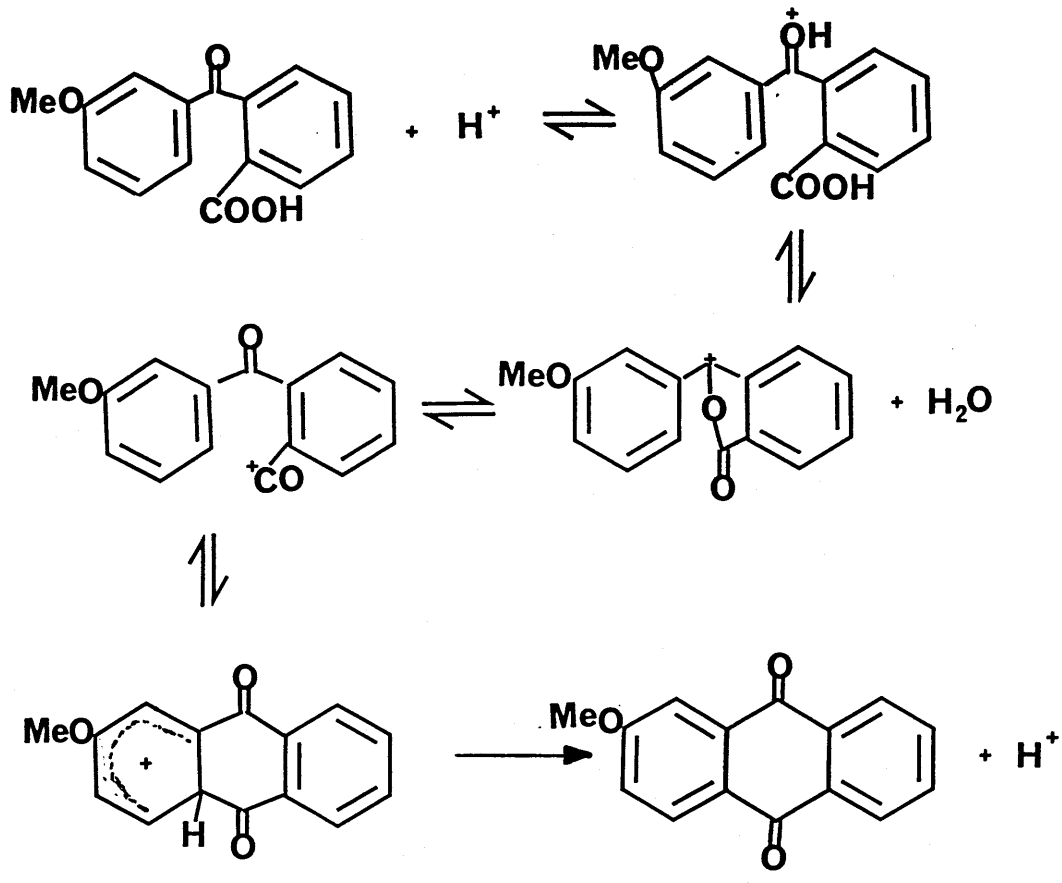
2-(4-methoxybenzoyl)benzoic acid - II

The next step in the mechanism after the formation of the lactol ion is its rearrangement to the free carboxonium ion III.



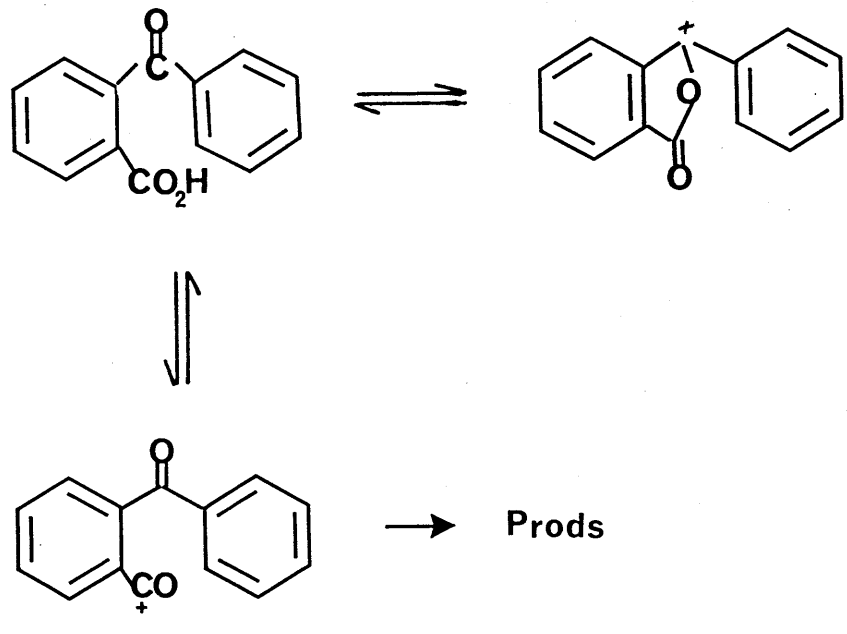
III

The free carboxonium ion (III) cannot be stabilised by the methoxy group in the benzoyl ring. The σ complex formed in the next step will also not gain much stabilisation from the methoxy group, as it is meta to the position of attack; hence the retarding effect. A full scheme of the suggested mechanism is given below for a 3-substituent in the benzoyl ring (Scheme 7.8a).



Scheme 7.8a

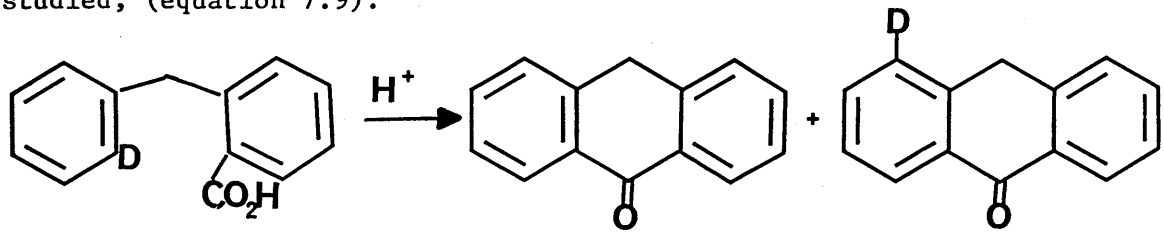
It is worth noting that the lactol carbonium ion is not necessarily involved in the reaction pathway, that is it can be written as an "aside" equilibrium (Scheme 7.8b).



Scheme 7.8b

The lactol carbonium ion is not kinetically significant at lower acid strengths where it is only formed in very small amounts. This is not the case, however, at higher acid strengths when substantial proportions of the substrate exist as the lactol carbonium ion.

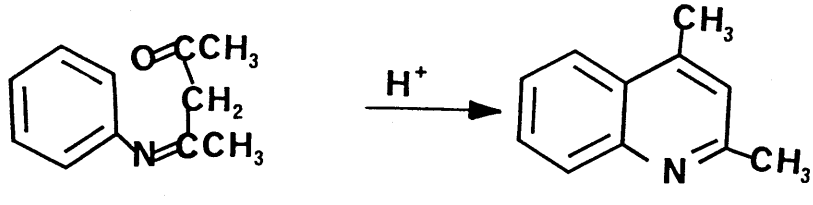
To determine whether proton loss in the last step was rate determining or not, the cyclisation of 2-(2'-deuterobenzoyl)benzoic acid was studied, (equation 7.9).[101b]



(7.9)

Analysis of the products indicated a definite isotope effect, the deuterated anthraquinone forming about 60% of the products. This implies that the decomposition of the σ complex could be partially rate limiting. This is dealt with in more detail in the discussion section.

Mechanistic studies on the cyclodehydration of 4-anilino-pent-3-en-2-ones (anils) have also been carried out.[102,103] The reaction follows the H_o acidity function with the rate limiting step being intramolecular electrophilic attack, (equation 7.10).



(7.10)

The cyclodehydration of 2-benzyl benzaldehydes to anthracenes has recently been investigated.[104] Once again the rates of reaction follow H_o. 2-Benzylbenzoic acids can be cyclised to produce anthrones but no

data on the mechanistic aspects of this cyclodehydration can be found in the literature.

Although most of these studies have been carried out in sulphuric acid, other reagents are now gaining more importance. Polyphosphoric (PPA) acid is often the catalyst of choice as no side sulphonation reactions are possible. Recently a paper was published giving details of the cyclisation of 3-arylbutanoic and 4-arylpropanoic acids to 1-indanones and 1-tetralones respectively, the catalytic reagent used being methanesulphonic acid.[105] The authors state that in some respects methanesulphonic acid is a superior reagent to PPA as a cyclising agent. This is due mainly to its acidity, good solvent properties, its convenience of use and reaction times being comparable to those in P.P.A.

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EXPERIMENTAL

Chapter 2 - Experimental

Nmr spectra were recorded on a Perkin Elmer R12B Nuclear Magnetic Resonance Spectrometer (^{1}H), a Joel FX90Q fourier transform nmr spectrometer (^{1}H, ^{13}C and ^{19}F), a Bruker WP60 fourier transform nmr spectrometer (^{1}H and ^{13}C) and on a Bruker WH400 courtesy of Warwick University.

Infrared spectra were recorded on a Pye Unicham SP1050 infrared spectrometer. Mass spectra were obtained by courtesy of PCMU Harwell on a VG ZAD 1F mass spectrometer. Melting points were determined using a Buchi 510 melting point apparatus and are uncorrected. Ultraviolet spectra were recorded on Pye Unicham SP8-100 and SP8-500 ultraviolet spectrophotometers.

Kinetic Measurements

Quartz ultra violet spectrophotometric cells (1cm) containing the required concentration of methanesulphonic, sulphuric or polyphosphoric acids were placed in a cell block maintained at the required temperature by means of a thermostat and allowed to reach thermal equilibrium. Stock solutions of all benzylbenzoic acids (25mg) were made in glacial acetic acid ($10cm^3$) except for 2(3-tolyl)-4,5-dimethoxybenzoic acid where diethylether (Na dried, $10cm^3$) was employed. This change was found to have no effect on the rate of reaction. After a suitable period small volumes of the stock solutions (10-15 μdm^3) were syringed into the UV cells to give a final concentration of the benzylbenzoic acids of about 10^{-4} mol dm^{-3}. The cells were then shaken thoroughly to ensure complete mixing before

being replaced in the instrument. The cyclisations were followed by measuring the change of absorbance with time at a wavelength close to the maximum in the U.V. spectrum of the product. Prior to kinetic studies each compound was cyclised in 100% methanesulphonic acid and the cyclisation followed by U.V. spectroscopy over the range 250-550 nm. For each compound an isobestic point was observed in these runs. The first order rate constants were calculated by a least squares method using at least 80% of the reaction. All kinetic runs were repeated at least once and reproducability was found to be ±5% at the maximum.

Procedure for Product Study

An accurately weighed sample (0.1 - 0.3g) of the benzylbenzoic acid was dissolved in the required acid ($30cm^3$), the flask sealed and partially immersed in a water bath maintained at the required temperature. The flask was removed after a period of about ten half-lives. The mixture was then poured onto ice and the resulting mixture extracted with dichloromethane ($5x20cm^3$). The organic layer was dried with $MgSO_4$ and, after filtering, was placed in a flask of known weight. The solvent was removed on a rotary evaporator and then under reduced pressure by means of a vacuum pump. The weight of the cyclised compound was obtained by reweighing the flask. The yields from product studies were in the region of 93-100%. Analysis of the product was carried out using nmr, GC and HPLC techniques.

2.1 Materials Used

Sulphuric Acid (98%) was an Analar reagent. Concentrations of diluted acids were determined using density measurements.[1]

Methanesulphonic acid (98%) was purchased from Fluka and purified by means of vacuum distillation through a six inch fractionating column packed with glass helices. The fraction collected boiling at 114°C at 0.5mm of mercury (lit.[1], b.p. 1mm 122°C). Dilute aqueous methanesulphonic acid was prepared by weighing, to three decimal places, the required amount of water and methanesulphonic acid separately in one piece of apparatus. On weighing the two reagents were allowed to mix whilst being cooled in ice.

Polyphosphoric acids were prepared from a standard polyphosphoric acid mixture obtained from B.D.H. Concentrations of dilute polyphosphoric acids were obtained from refractive index measurements.[2]

Acetic acid was an Analar reagent purchased from the Aldrich Chemical Co. Ltd. and was used without further purification.

Trifluoromethanesulphonic acid was purchased from the Aldrich Chemical Co. Ltd. and used without further purification.

Magic Acid was a spectrograde reagent purchased from the Aldrich Chemical Co. Ltd. and was used without further purification.

Sulphurylchloride fluoride was a spectrograde reagent purchased from the Aldrich Chemical Co. Ltd. and was used without further purification.

Trichlorofluoromethane was purchased from Fluka, b.p. 24°C (lit.[1], b.p. 24°C) and used without further purification.

2-Chloroanthraquinone was purchased from the Aldrich Chemical Co. Ltd., m.p. 209-211°C (lit.[1], m.p. 211°C) and used without further purification.

1-Chloroanthraquinone was purchased from the Aldrich Chemical Co. Ltd., m.p. 159-160°C (lit.[1], m.p. 162°C) and used without further purification.

Anthrone was purchased from the Aldrich Chemical Co. Ltd., m.p. 152-154°C (lit.[1], m.p. 155°C) and used without further purification.

1-Methoxyanthraquinone A sample was kindly donated by ICI plc. and used without further purification.

Methanesulphonic Anhydride was purchased from Fluorochem Ltd. It was recrystallised from sodium dried diethyl ether giving white needles m.p. 69-70°C (lit.[1], m.p. 71°C).

2-Benzylbenzoic acid (compound I) was purchased from the Aldrich Chemical Co. Ltd. It was recrystallised from dilute ethanol giving white needles m.p. 116-118°C (Lit.[1], m.p. 118°C).

4-Methylbenzhydrol was purchased from the Aldrich Chemical Co. Ltd. It was purified by recrystallisation from ligroin giving white needles m.p. 52-54°C (lit.[3], m.p. 52-53°C).

Preparation of 2(3-toluoyl)benzoic acid This was prepared by a

modified method of that of Weizmann et al.[4] To a stirred solution of phthalic anhydride (23g) in dry tetrahydrofuran (100cm^3) under a nitrogen atmosphere, was slowly added, over a period of one hour, a Grignard solution prepared using 3-bromotoluene (30g) and magnesium (4.2g) in dry diethyl ether (70cm^3). The reaction mixture was then boiled under reflux for four hours. After cooling the mixture was quenched with water and hydrochloric acid and then extracted with diethyl ether (5x30cm^3). The resulting ethereal solution was extracted with 10% sodium hydroxide solution (4x25cm^3). Neutralisation of this basic solution with concentrated hydrochloric acid gave a white precipitate which was extracted with chloroform (5x40cm^3). After drying the chloroform solution ($MgSO_4$) the solvent was removed to give 2(3-toluoyl)benzoic acid. This was recrystallised from toluene giving white needles, m.p. 159-161°C (lit.[1], m.p. 162.2-162.4°C).

2(3-Toluoyl)benzoic acid was also prepared by the method of Pharam et al.[12,13,14] O-Bromobenzoic acid, (5g, 25mmol) was dissolved in 50cm^3 of tetrahydrofuran (freshly distilled over calcium hydride) in a three-neck flask fitted with a low temperature thermometer, two addition funnels, magnetic stirrer bar and nitrogen inlet tube. The mixture was stirred using a magnetic stirrer and allowed to cool to -100°C in a liquid nitrogen-ether bath. n-Butyllithium (25cm^3 of 2M solution in hexane (50mmol)) was added at such a rate as to maintain the temperature at -100°C. On completion of addition the mixture was stirred for a further twenty minutes at -100°C. m-Toluoyl chloride (4g dissolved in 10ml of dry tetrahydrofuran) was then slowly added, the temperature never being allowed to rise above -95°C. The mixture was then kept at -100°C for a further two hours with constant stirring. After allowing the mixture to warm up to room temperature it was poured into 100cm^3 of 5% hydrochloric acid and stirred for 30 minutes. The

organic layer was then separated and the aqueous layer extracted with dichloromethane ($4x50cm^3$). The organic layers were combined and washed with water ($2x25cm^3$), and extracted with 10% sodium hydroxide ($3x75cm^3$). The alkaline extracts were acidified with hydrochloric acid and the organic acids extracted with dichloromethane ($4x50cm^3$). After drying the dichloromethane solution ($MgSO_4$) the solvent was removed to give 2(3-toluoyl)benzoic acid. The yield was 10%.

Preparation of 2(3-tolyl)benzoic acid (Compound II)

2,(3-Tolyl)benzoic acid was prepared from 2(3-toluoyl)benzoic acid by means of a Clemmensen reduction. To a mixture of zinc amalgam (100g zinc and 8g mercury (II) chloride[5] in $75cm^3$ of water and $100cm^3$ of hydrochloric acid) was added toluoylbenzoic acid (20g) and toluene ($20cm^3$). The mixture was boiled under reflux for about thirty hours during which time concentrated hydrochloric acid was added every four hours ($30cm^3$ each time). On cooling, the reaction mixture was extracted with dichloromethane ($5x20cm^3$). This was in turn extracted with 10% sodium hydroxide ($4x15cm^3$). The alkaline solution was neutralised with hydrochloric acid to give a white precipitate which was extracted with dichloromethane ($5x20cm^3$). After drying the dichloromethane solution ($MgSO_4$) the solvent was removed to give 2(3-tolyl)benzoic acid.

2(3-Tolyl)benzoic acid (yield 26%) was recrystallised from toluene to give white needles m.p. 106-107°C. Calculation for $C_{15}H_{14}O_2$: C, 79.65; H, 6.19; found C, 79.54; H, 6.26; ν max (nujol) 2940 and $2860cm^{-1}$, (C=O) $1690cm^{-1}$; δ ($CDCl_3$) 8.12-7.99 (m, 1H), 7.50-7.00 (m, 7H) 4.41 (S, 2H), 2.28 (S, 3H).

2(3-Methoxybenzyl)benzoic acid (Compound III) was prepared from 3-bromoanisole and phthalic anhydride using the method outlined for the preparation of 2(3-tolyl)benzoic acid.

2(3-Methoxybenzyl)benzoic acid (yield 27%) was recrystallised from toluene to give white needles, m.p., 97-98°C. $C_{15}H_{14}O_3$ requires: C, 74.38%; H, 5.78%: found C, 74.07%; H, 5.91%; ν max (nujol) 2860 and 2940cm^{-1}, (C=O) 1683^{-1}; $\delta(CDCl_3)$ 8.11-7.99 (M, 1H), 7.48-6.69 (M, 7H), 4.42 (S, 2H), 3.71(S, 3H).

2(3-Chlorobenzyl)benzoic acid (Compound IV) was prepared from 3-bromochlorobenzene and phthalic anhydride using the method outlined for 2(3-tolyl)benzoic acid.

2(3-Chlorobenzyl)benzoic acid (yield 18%) was recrystallised from toluene to give white needles m.p. 105-106°C. $C_{14}H_{11}ClO_2$ requires C, 68.15%; H, 4.46%: found C, 68.00%; H, 4.41%; ν max (nujol) 2860 and 2940cm^{-1}; (C=O) 1690cm^{-1}; $\delta(CDCl_3)$ 8.199-8.097 (M, 1H), 7.645-7.016 (M, 7H), 4.473 (S, 2H).

2(3-Fluorobenzyl)benzoic acid (Compound V) was prepared from 3-bromofluorobenzoic and phthalic anhydride using the method outlined for 2-(3-tolyl)benzoic acid.

2(3-Fluorobenzyl)benzoic acid (yield 14%) was recrystallised from toluene to give white needles, m.p. 113.5-114.5°C. $C_{14}H_{11}FO_2$ requires: C, 73.04; H, 4.78; found C, 73.44; H, 4.78; ν max (nujol) 2940 and 2860cm^{-1}, (C=O) 1690cm^{-1}; ($CDCl_3$) 8.190-8.086 (M, 1H), 7.640-6.825 (M, 7H), 4.487 (S, 2H).

2(3-Hydroxybenzyl)benzoic acid (Compound VI) was prepared from 2(3-methoxybenzyl)benzoic acid and constant boiling hydroiodic acid using the method outlined for the preparation of 2(4-hydroxybenzyl) benzoic acid.

2(3-Hydroxybenzyl)benzoic acid (yield 48%) was recrystallised from a 3:1 mixture of ether-pet ether (40-60) to give very pale green crystals, m.p. 140-142°C. $C_{14}H_{12}O_3$ requires C, 73.69; H, 5.27; found C, 73.62; H, 5.12; ν max (nujol) 2940 and 2860cm^{-1}, (C=O) 1700cm^{-1}, $\delta(CDCl_3)$ 8.15-8.01 (M,1H); 7.42-6.71 (M,7H); 4.41 (S, 2H).

2(4-Tolyl)benzoic acid (Compound VII) was prepared from 4-bromotoluene and phthalic anhydride using the method outlined for 2(3-tolyl)benzoic acid.

2(4-Tolyl)benzoic acid (yield 29%) was recrystallised from toluene to give white needles m.p. 132-133°C. $C_{15}H_{14}O_2$ requires C, 79.65; H, 6.19; found C, 79.92; H, 6.28; ν max (nujol) 2860 and 2940cm^{-1}, (C=O) 1677cm^{-1}; $\delta(CDCl_3)$ 7.942-9.921 (M, 1H), 7.856-7.018 (M, 7H), 4.351 (S, 2H), 2.245 (S, 3H).

2(4-Methoxybenzyl)benzoic acid (Compound VIII) was prepared from 4-bromoanisole and phthalic anhydride using the method outlined for the preparation of 2(3-tolyl)benzoic acid.

2(4-Methoxybenzyl)benzoic acid (yield 30%) was recrystallised from toluene giving white needles, m.p. 115-117°C. $C_{15}H_{14}O_3$ requires C, 74.38; H, 5.78; found C, 74.71; H, 5.89; ν max (nujol) 2860 and 2940cm^{-1}, (C=O) 1683cm^{-1}; $\delta(CDCl_3)$ 7.962-7.856 (M, 1H), 7.476-6.678 (M, 7H), 4.343 (S, 2H), 3.709 (S, 3H).

2(4-Chlorobenzyl)benzoic acid (Compound IX) was prepared from 4-bromochlorobenzene and phthalic anhydride using the method outlined for the preparation of 2(3-tolyl)benzoic acid.

2(4-Chlorobenzyl)benzoic acid (yield 21%) was recrystallised from toluene to give white needles, m.p. 128-130°C. $C_{14}H_{11}ClO_2$ requires C, 68.15; H, 4.46; found C, 68.41; H, 4.45; ν max (nujol) 2860 and 2940cm^{-1}, (C=O) 1667cm^{-1}, δ ($CDCl_3$) 8.048-7.942 (M, 1H), 7.504-7.009 (M, 7H), 4.384 (S, 2H).

2(4-Fluorobenzyl)benzoic acid (Compound X) was prepared from 4-bromofluorobenzene and phthalic anhydride using the method outlined for the preparation of 2(3-tolyl)benzoic acid.

2(4-Fluorobenzyl)benzoic acid (yield 15%) was recrystallised from toluene giving white needles, m.p. 120-122°C. $C_{14}H_{11}FO_2$ requires C, 73.04; H, 4.78; found C, 73.26; H, 4.58; ν max (nujol) 2860 and 2940cm^{-1}, (C=O) 1683cm^{-1}; δ ($CDCl_3$, DMSO, $-D_6$) 8.122-8.020 (M, 1H), 7.566-6.813 (M, 7H), 4.404 (S, 2H).

Preparation of 2(4-hydroxybenzyl)benzoic acid (Compound XI) To a solution of 2(4-methoxybenzyl)benzoic acid (0.5g) in glacial acetic acid (10cm^3) was added 0.5cm^3 of constant boiling hydroiodic acid. The mixture was refluxed for two hours and then treated with enough sodium thiosulphate solution to remove the iodine. Any sulphur formed was filtered off and the solvents removed to give 2(4-hydroxybenzyl) benzoic acid and inorganic salts. 2(4-hydroxybenzyl)benzoic acid was extracted with dichloromethane (4x10cm^3). After drying the dichloromethane solution ($MgSO_4$) the solvent was removed to give 2(4-hydroxybenzyl)benzoic acid.

2(4-Hydroxybenzyl)benzoic acid (yield 63%) was recrystallised from a 3:1 mixture of ether-pet ether (40-60) to give white needles, m.p. 149-151°C. $C_{14}H_{12}O_3$ requires C, 73.69; H, 5.27; found C, 73.68; H, 5.29; ν max (nujol) 2940 and 2860cm^{-1}, (C=O) 1695cm^{-1}; $\delta(CDCl_3)$ 7.91-8.03 (M, 1H), 6.7-7.41 (M, 7H), 4.33 (S, 2H).

Preparation of 2(2-deuterobenzyl)benzoic acid (Compound Ia)

2-Deuterochlorobenzene was prepared by quenching a solution of the Grignard reagent made from 2-bromochlorobenzene (30g) and magnesium (4.1g) in diethylether (60cm^3), with an excess of deuterium oxide. This was followed by the addition of hydrochloric acid and extraction with diethylether (4x20cm^3). After drying the ethereal solution ($MgSO_4$), the solvent was removed to give crude 2-deuterochlorobenzene. This was purified by distillation, collecting the fraction boiling between 130-134°C.

2-Deuterobenzylbenzoic acid was prepared from 2-deuterochlorobenzene using the method outlined for the preparation of 2(3-tolyl)benzoic acid. However, in this case the Grignard solution was prepared in tetrahydrofuran rather than diethylether.

This gave 2-deuterobenzylbenzoic acid (19%) which was recrystallised from ether-pet ether (40-60) to give white needles, m.p. 116-117°C. $C_{14}H_{11}DO_2$ requires: C, 78.87: H, 5.16: found C, 78.62%; H, 5.44%; ν max (nujol) 2860 and 2940cm^{-1}, (C=O) 1695cm^{-1}; $\delta(CDCl_3)$ 8.11-7.99 (M, 1H), 7.51-7.12 (M, 7H), 4.45 (S, 2H). m.s. m/z 213 (M^+, 24.55%), 196 (15.95), 195 (100), 194 (49.36), 167 (10.11), 166 (51.71), 165 (15.76). No peak observed at m/z 212 (intensity limit 0.04% of base).

Preparation of 2(3-tolyl)-4,5-dimethylbenzoic acid (Compound XII)

4,5-Dimethylphthalic anhydride was prepared by the Diels-Alder condensation of 2,3-dimethylbutadiene with maleic anhydride.[6]

The resulting product (10g) and 10% Pd-charcoal (0.5g) in m-xylene ($50cm^3$) were boiled under reflux for 48 hours. The solution was filtered whilst still hot and on cooling gave crystals of 4,5-dimethyl phthalic anhydride, m.p. 207-208°C (lit.[3], m.p. 207-209°C).

2(3-Tolyl)-4,5-dimethylbenzoic acid was prepared from 4,5-dimethyl phthalic anhydride and 3-bromotoluene using the method outlined for the preparation of 2(3-tolyl)benzoic acid. 2(3-Tolyl)-4,5-dimethylbenzoic acid (yield 11%) was recrystallised from benzene to give white crystals m.p. 124-126°C. $C_{17}H_{18}O_2$ requires C, 80.31; H, 7.09; found C, 80.12; H, 7.33; ν max (nujol) 2860 and 2940cm^{-1}, (C=O) 1685cm^{-1}; δ($CDCl_3$/DMSO-D_6) 7.778 (S, 1H), 7.103-6.969 (M, 5H), 4.337 (S, 2H), 2.264 (S, 3H), 2.212 (S, 3H).

Preparation of 2(3-tolyl)-4,5-dimethoxybenzoic acid (Compound XIII)

4,5-Dimethoxyphthalic anhydride was prepared by the method of Edwards et al.[7]

2(3-Tolyl)-4,5-dimethoxybenzoic acid was prepared from 3-bromotoluene and 4,5-dimethoxyphthalic anhydride using the method outlined for the preparation of 2(3-tolyl)benzoic acid. 2(3-Tolyl)-4,5-dimethoxybenzoic acid (yield 12%) was recrystallised from n-dibutyl ether giving white needles m.p. 156-157°C. $C_{17}H_{18}O_4$ requires C, 71.33; H, 6.29; found C, 71.45; H, 6.28; ν max (nujol) 2860 and 2940cm^{-1}, (C=O) 1687cm^{-1}; δ($CDCl_3$) 7.623 (S, 1H), 7.247-6.9, (M, 4H), 6.664 (S, 1H), 4.413 (S, 2H), 3.918 (S, 3H), 3.833 (S, 3H), 2.296 (S, 3H).

Preparation of 2(3-tolyl)-4,5-dichlorobenzoic acid (Compound XIV) 4,5-Dichlorophthalic anhydride was prepared by boiling under reflux 4,5-dichlorophthalic acid (30g) and redistilled acetic anhydride ($100cm^3$) for two hours. On cooling 4,5-dichlorophthalic anhydride was obtained as white crystals and used without further purification in the next step.

2(3-Tolyl)-4,5-dichlorobenzoic acid was prepared from 4,5-dichlorophthalic anhydride and 3-bromotoluene using the method outlined for the preparation of 2(3-tolyl)benzoic acid. 2(3-Tolyl)-4,5-dichlorobenzoic acid (yield 6%) was recrystallised from benzene giving white crystals, m.p. 155-156°C. $C_{15}H_{12}Cl_2O_2$ requires C, 61.02; H, 4.01; found C, 60.88; H, 3.96; ν max (nujol) 2860 and $2940cm^{-1}$, (C=O) $1695cm^{-1}$; δ ($CDCl_3$/DMSO-d_6) 8.149 (S, 1H), 7.285-6.961 (M, 5H), 4.348 (S, 2H), 2.313 (S, 3H).

Preparation of 2(3-tolyl)-4,5-diphenylbenzoic acid (Compound XV) 4,5-Diphenylphthalic anhydride was prepared by a Diels-Alder condensation. To anhydroacetone-benzil (10g) was added acetylene dicarboxylic acid (5g) and the mixture heated with stirring to 140°C. This temperature was maintained for ten minutes. After cooling, enough dichloromethane was added to dissolve all the solid. The organic solution was then extracted with 10% sodium hydroxide ($3x25cm^3$). Neutralisation of this basic solution with concentrated hydrochloric acid gave a pale yellow precipitate which was extracted with dichloromethane ($5x20cm^3$). After drying the dichloromethane solution ($MgSO_4$), the solvent was removed to give 4,5-diphenylphthalic acid. This was converted to the anhydride by boiling under reflux with redistilled acetic anhydride for two hours. On cooling this gave brown crystals of 4,5-diphenylphthalic anhydride, m.p. 150-152°C (lit.[9] m.p.

150-151°C).

2(3-Tolyl)-4,5-diphenylbenzoic acid was prepared from 4,5-diphenyl phthalic anhydride and 3-bromotoluene using the method outlined for 2(3-tolyl)benzoic acid. However, in this case the reaction mixture consisting of the Grignard solution and the 4,5-diphenylphthalic acid was refluxed for eighteen hours rather than four hours.

2(3-Tolyl)-4,5-diphenylbenzoic acid (yield 8%) was recrystallised from n-dibutyl ether giving white needles, m.p. 200-201°C. $C_{27}H_{22}O_2$ requires C, 85.71; H, 5.82; found C, 85.77; H, 5.91; νmax (nujol) 2940 and 2860cm^{-1}, (C=O) 1700cm^{-1}; δ ($CDCl_3$/DMSO,d_6) 8.157 (S, 1H), 7.323-7.179 (M, 15H), 4.493 (S, 2H), 2.299 (S, 3H).

Preparation of 2(2,6-dimethylbenzyl)benzoic acid (Compound XVI)

2(2,6-Dimethylbenzyl)benzoic acid was prepared from 2-bromo-m-xylene and phthalic anhydride using the method outlined for 2(3-tolyl)benzoic acid.

2(2,6-Dimethylbenzyl)benzoic acid (yield 5%) was recrystallised from toluene to give white crystals, m.p. 206-207°C. $C_{16}H_{16}O_2$ requires C, 80.00; H, 6.67; found C, 79.87; H, 6.69; ν max (nujol) 2950 and 2860cm^{-1}, (C=O) 1690cm^{-1}; δ ($CDCl_3$/DMSO,d_6) 8.048-7.946 (M, 1H), 7.267-6.621 (M, 6H), 4.457 (S, 2H), 2.163 (S, 6H).

2-Phenethylbenzoic acid was prepared from phenylacetic acid and phthalic anhydride using the method of Van der Stelt et al.[10]

2-Phenethylbenzoic acid was recrystallised from a 3:1 mixture of pet-ether (40-60) and ether to give white crystals, m.p. 129-131°C (lit.[10],

m.p. 130-131°C).

Bis(2-methylphenyl)methanol was prepared by the method of Boyd et al.[11] Bis(2-methylphenyl)methanol was recrystallised from ethanol giving white needles m.p. 119-120°C (lit. 3, m.p. 119-119.5°C).

Tri-m-chlorophenyl carbinol was prepared by the method of Marvel and Johnston.[15] Tri-m-chlorophenyl carbinol was purified by column chromotography using silica and a 10:1 mixture of hexane and ether. $C_{19}H_{13}Cl_3O$ requires C, 62.72; H, 3.58; found C, 62.65; H, 3.49; ($CDCl_3$) 7.307-7.081 (M, 12H), 2.806, (S, 1H).

2-(2-Naphthoyl)benzoic acid was prepared by the method of Weizman.[4] 2-(2-Naphthoyl)benzoic acid was recrystallised from toluene to give white crystals, m.p. 166-167°C (lit.[4], m.p. 168°C).

2(2-Toluoyl)benzoic acid was prepared from 2-bromotoluene and phthalic anhydride using the method outlined for the preparation of 2(3-toluoyl) benzoic acid. 2(3-Toluoyl)benzoic acid was recrystallised from toluene to give white crystals, m.p. 130-131°C (lit.[3], m.p. 128-130°C).

2,3-Dephenylbutan-2,3-diol was prepared by irradiating a solution of acetophenone (50g) in Propan-2-ol ($1.5dm^3$) over a period of twenty four hours with ultraviolet light. On removal of the solvent almost pure 2,3-diphenylbutan-2,3-diol (49.5g) was obtained giving a yield of over 98%. Without further purification a m.p. of 118-120°C (lit.[1], m.p. 121-2°C) was obtained.

2,3-Diphenylbuta-1,3-diene[16] was prepared by vacuum distillation of 2,3-diphenylbutan-2,3-diol (20g) in the presence of powdered dry

potassium hydrogen sulphate (30g). A yellow oily solid (5g) was collected and had a m.p. of 48-50°C (lit.[16], 50-51°C).

2,3-Diphenylbuta-1,3-diene (5g) was then refluxed with maleic anhydride (2g) in toluene for two hours. Evaporation of the solvent yielded 4,5-diphenyltetrahydro-phthalic anhydride m.p. 162-164 (lit.[16], m.p. 164-5°C). This could not be converted to the 4,5-diphenylphthalic anhydride by 10% Pd/C in the presence of (i) xylene (ii) p-cymene and (iii) o-dichlorobenzene.

4-Chloro-2-bromobenzoic acid was prepared by carrying out the Sandmeyer reaction on 4-chloro-2-aminobenzoic acid using hydrobromic acid and cuprous bromide. 4-Chloro-2-bromobenzoic acid was recrystallised from ethanol giving needles m.p. 158-160°C (lit.[3] 159-160°C).

4-Nitro-2-bromobenzoic acid was prepared by oxidation of 4-nitro-2-bromotoluene by acidified potassium permanganate.

4-Nitro-2-bromobenzoic acid was recrystallised from water giving yellow needles m.p. 164-166°C (lit.[3], m.p. 166°C).

Table 2.1 Names of compounds studied and their code numbers together with the wavelengths used for kinetic studies

Name	Number	Wavelengths used for kinetics /nm
2-Benzylbenzoic acid	I	346
2(2-Deuterobenzyl)benzoic acid	Ia	346
2(3-Tolyl)benzoic acid	II	360
2(3-Methoxybenzyl)benzoic acid	III	400
2(3-Chlorobenzyl)benzoic acid	IV	350
2(3-Fluorobenzyl)benzoic acid	V	355
2(3-Hydroxybenzyl)benzoic acid	VI	400
2(4-Tolyl)benzoic acid	VII	350
2(4-Methoxybenzyl)benzoic acid	VIII	340
2(4-Chlorobenzyl)benzoic acid	IX	340
2(4-Fluorobenzyl)benzoic acid	X	338
2(4-Hydroxybenzyl)benzoic acid	XI	340
2(3-Tolyl)-4,5-dimethylbenzoic acid	XII	380
2(3-Tolyl)-4,5-dimethoxybenzoic acid	XIII	420
2(3-Tolyl)-4,5-dichlorobenzoic acid	XIV	375
2(3-Tolyl)-4,5-diphenylbenzoic acid	XV	400
2(2,6-Dimethylbenzyl)benzoic acid	XVI	N/A

Determination of Acidity Function H_R

Acidity function studies were carried out on methanesulphonic acid to determine the acidity function H_R from 92% to 100%. The technique

employed involved the use of ultra violet spectrophotometry and relies on the principle that at a given wavelength the measured absorption of the acid-indicator solution will be the sum of the absorption of both the free base and the conjugate acid. All measurements were made at the wavelength of maximum absorption for the conjugate acid.

For each measurement the following procedure was employed. The required strength of methanesulphonic acid was prepared as outlined earlier. This was then used to calibrate the ultraviolet spectrophotometer at the required temperature (25.0°C ± 0.1) and the required wavelength. The indicator was then accurately weighed (0.02g) in a $10cm^3$ volumetric flask of known weight. To this was added the required methanesulphonic acid (15g) and the final weight of the flask recorded. On thorough shaking of the mixture (to ensure a homogeneous solution) a portion of the solution (2g) was transferred to another volumetric flask of known weight and the flask reweighed. To this was added some more of the methanesulphonic acid (10g) and the total weight of the flask recorded. After thorough mixing a portion of this solution (2g) was transferred to a third $10cm^3$ volumetric flask of known weight and the flask reweighed. The appropriate methanesulphonic acid was then added such that the total volume was exactly $10cm^3$. This resulted in a solution of known concentration with respect to the indicator. In each case this was about $10^{-4}M$.

The final solution was placed in an ultra-violet quartz cell (1cm) and its absorbence recorded at the desired wavelength. For indicators that decomposed with time on addition of acid a stopwatch was used to record the time from the moment of mixing and the absorbance monitored for about 10 minutes. The time zero absorbence for this solution was then obtained by extrapolation.

A plot of (extinction coefficient, obtained from the Beer Lambert's law) against % methanesulphonic acid resulted in a sigmoidal curve from which the relative concentrations of the free base and the conjugate acid can be obtained, (Fig. 2.1). The ratio I, $[BH^+]/[B]$, can hence be determined.

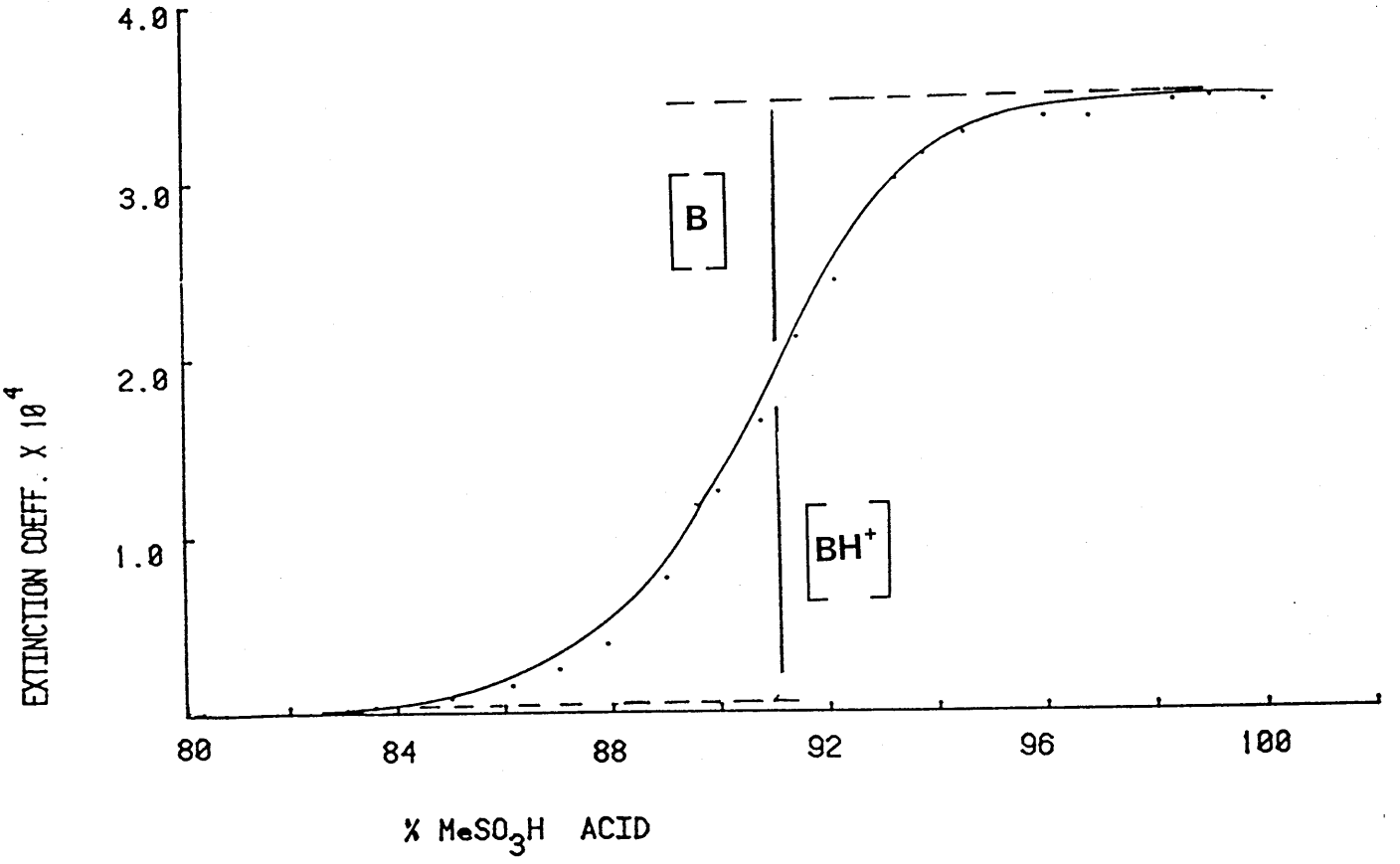

Fig. 2.1

References for Experimental

1. Handbook of Chemistry and Physics, 60th Edition, CRC Press, 1980.
2. R.G. Downing and D.E. Pearson, J. Am. Chem. Soc., 83, 1718 (1961)
3. Dictionary of Organic Compounds, 5th Edition, Chapman and Hall, 1982.
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5. A. Vogel, Text Book of Practical Organic Chemistry, 4th Edition, (1979), p318.
6. A. Vogel, Text Book of Practical Organic Chemsitry, 4th Edition, (1979), p867.
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8. F.R. Japp and C.I. Burton, J. Chem. Soc., 51, 428 (1887)
9. H.P. Huggill and A. Parkinson, Brit., 683, 770, Dec. 3, 1952.
10. C. Van Der Stelt, et al., J. of Med. and Pharm. Chem., 4(2), 335-349, (1961)
11. D.R. Boyd, et al., J. Chem. Soc., 908 (1927)
12. W.E. Parham and L.D. Jones, J. Org. Chem., 41, 1187 (1976)
13. W.E. Parham and Y.A. Sayed, J. Org. Chem., 39, 2051 (1974)
14. W.E. Parham et al., J. Org. Chem., 46, 1057 (1981)
15. C.S. Marvel et al., J. Am. Chem. Soc., 66, 914-18 (1944)
16. See Chem. Abs., 45, 4684i (1951).

RESULTS AND DISCUSSION

Chapter 3 - Results and Discussion

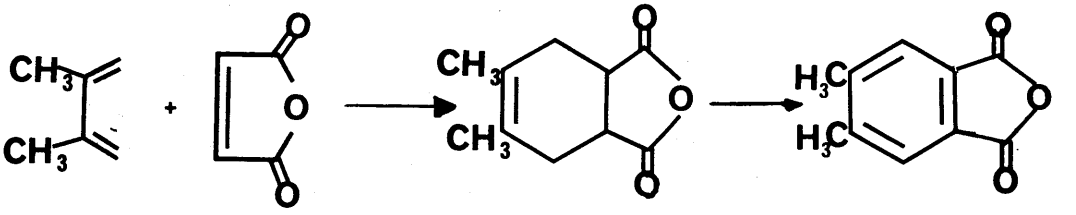
3.1 Synthesis of Benzylbenzoic Acids

Benzylbenzoic acids can be synthesised using a number of different routes. The common feature of nearly all of these routes is the initial synthesis of the corresponding benzoylbenzoic acid. In this project the benzoylbenzoic acids were synthesised using the route of Weizmann et al.,[1] which involved the reaction of a bromobenzene Grignard with phthalic anhydride. The main reasons for choosing this method were: i) the relatively good yields, ii) the control of the position of the substituent in the benzyl ring, iii) a relatively straightforward reaction to carry out in the laboratory, and iv) the low cost and commercial availability of the starting materials. This method produced the appropriate benzoylbenzoic acid in yields of 35-55%, but the conversion of this acid to the required benzylbenzoic acid via the Clemmensen method reduced the overall yield to about 10-20%. Reduction was also carried out using the Wolff-Kishner method and hydroiodic acid and red phosphorous. In both cases the yields obtained were much poorer in comparison with the Clemmensen method. For all the benzylbenzoic acids substituted in the benzyl ring the corresponding substituted bromobenzene was commercially available. The only benzylbenzoic acids substituted in the benzyl ring not made by this method were the hydroxy derivatives which were made from the corresponding methoxy compounds using hydroiodic acid.

Apart from the low yield obtained in the Clemmensen reduction the only other synthetic problem encountered in this work was the preparation of disubstituted phthalic anhydrides which were the precursors for the synthesis of benzylbenzoic acids with substituents in the benzoic acid

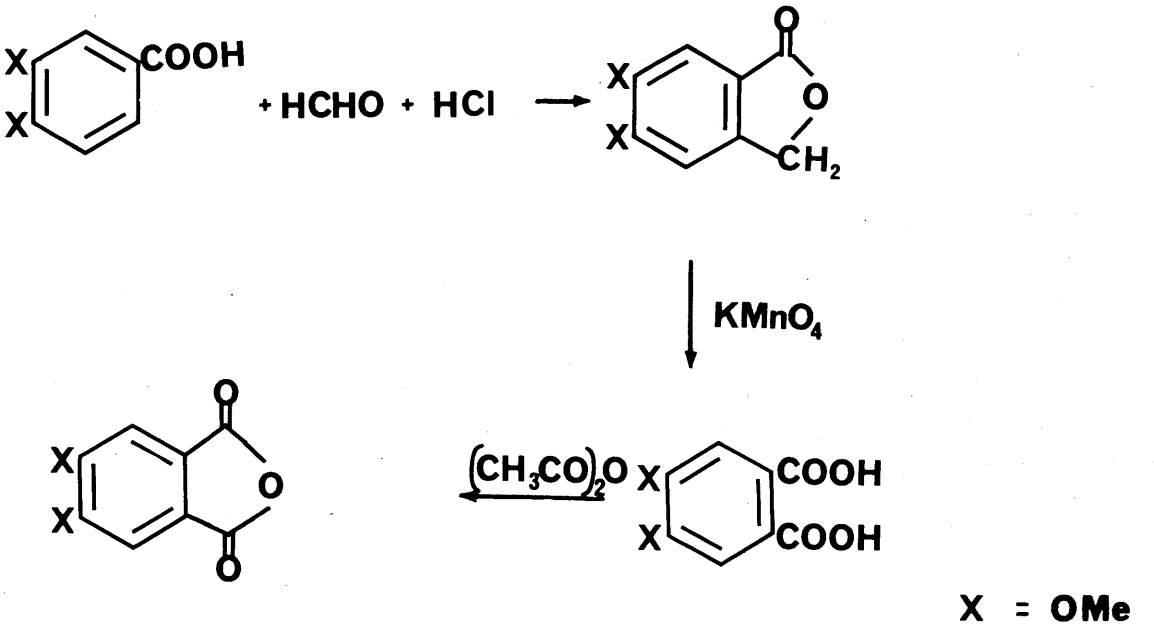
ring.

4,5-Dichlorophthalic anhydride was prepared from the corresponding diacid. 4,5-Dimethylphthalic anhydride was prepared as shown in scheme 3.1. The Diels-Alder adduct of 2,3-dimethylbuta-1,3-diene and maleic anhydride was dehydrogenated by 10% palladium charcoal in boiling xylene to give the anhydride.



Scheme 3.1

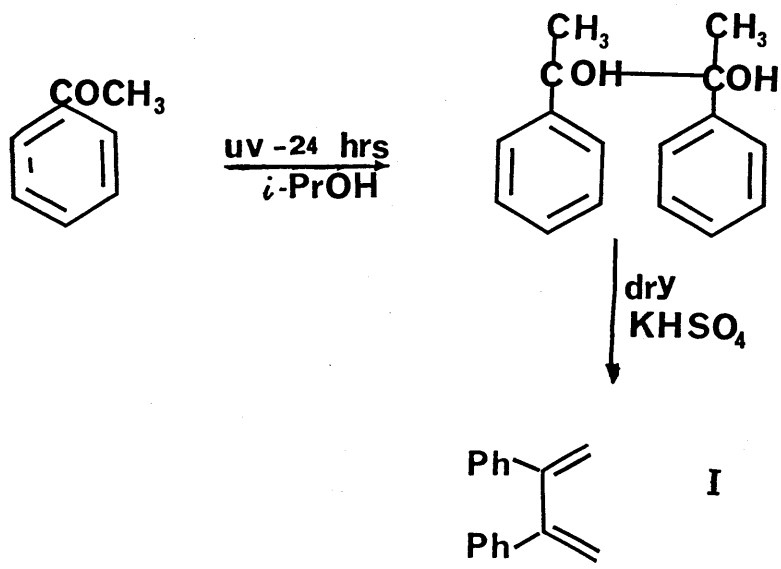
4,5-Dimethoxyphthalic anhydride was prepared by the method of Edwards et al.,[2] (Scheme 3.2).



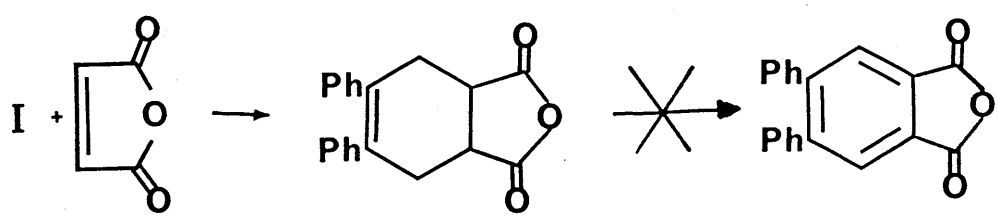
Scheme 3.2

Of the disubstituted phthalic anhydrides the most difficult to prepare was 4,5-diphenylphthalic anhydride. Attempts were made to synthesise this compound via 2,3-diphenyl-1,3-butadiene, but yields were very

poor. The first step in the synthesis of 2,3-diphenylbuta-1,3-diene involved the preparation of the dimer of acetophenone. This was achieved by a free radical reaction using ultraviolet light over 24 hours with propan-2-ol as the solvent.[3] The yield was over 98%. The butadiene was distilled under vacuum over dry potassium hydrogensulphate, however polymerisation reduced the overall yield (Scheme 3.3).



Scheme 3.3

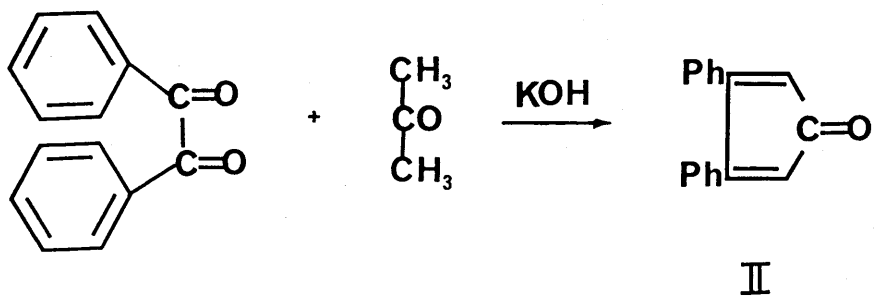


Scheme 3.3a

The butadiene was coupled with maleic anhydride in a Diels-Alder

reaction and although this gave a good yield of the cyclohexene derivative, it was not possible to dehydrogenate it further to produce 4,5-diphenyl phthalic anhydride (Scheme 3.3a).

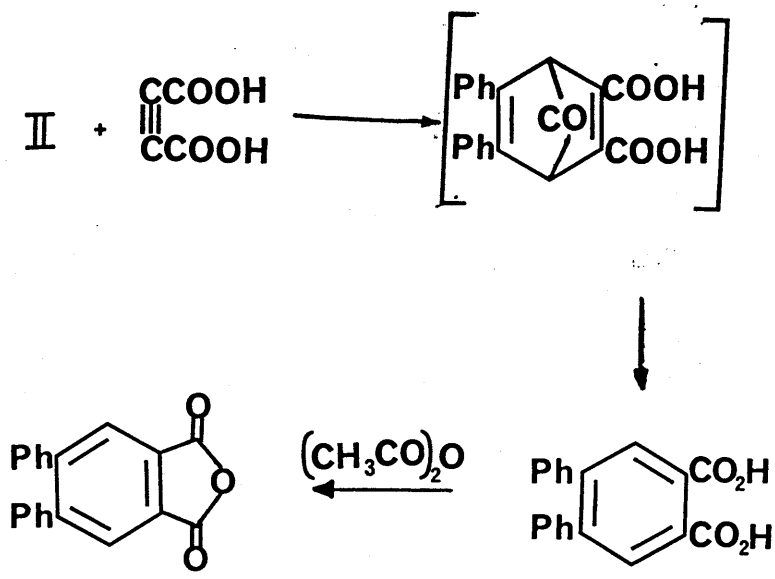
This dehydrogenation step was attempted using a palladium charcoal catalyst in a range of high boiling solvents such as nitrobenzene, o-dichlorobenzene and p-cymene. As an alternative route, anhydroacetonebenzil[4] was reacted with acetylenedicarboxylic acid using a Diels-Alder reaction. Anhydroacetonebenzil[4] was prepared by reacting benzil with acetone in the presence of potassium hydroxide solution (Scheme 3.4).



II

Scheme 3.4

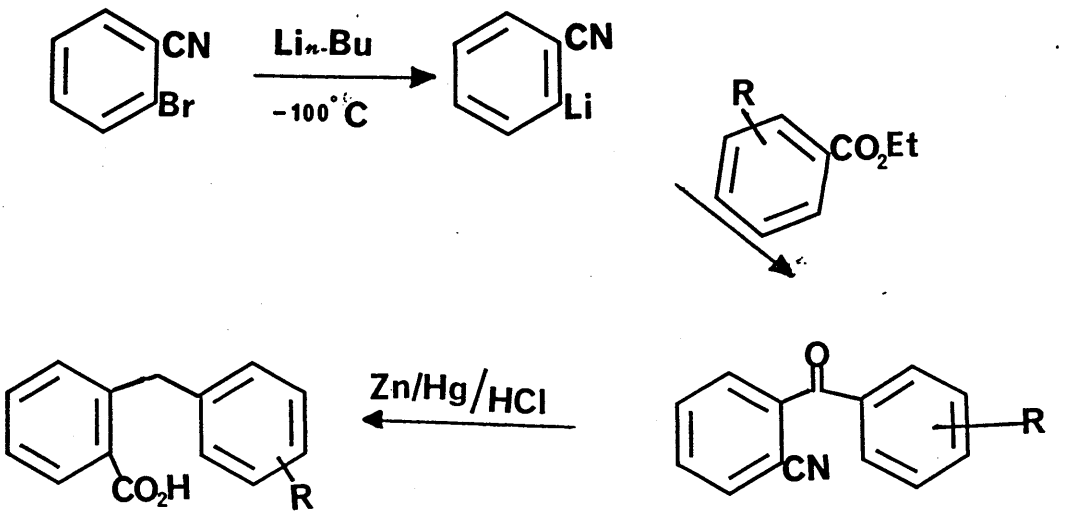
The Diels-Alder reaction was carried out in i) o-dichlorobenzene ii) p-cymene iii) p-xylene, but all attempts proved to be unsuccessful. However, when the reaction was performed in the absence of solvent and with fine temperature control, 4,5-diphenylphthalic acid was obtained in 49% yield (Scheme 3.4a). This was converted to the phthalic anhydride using acetic anhydride.



Scheme 3.4a

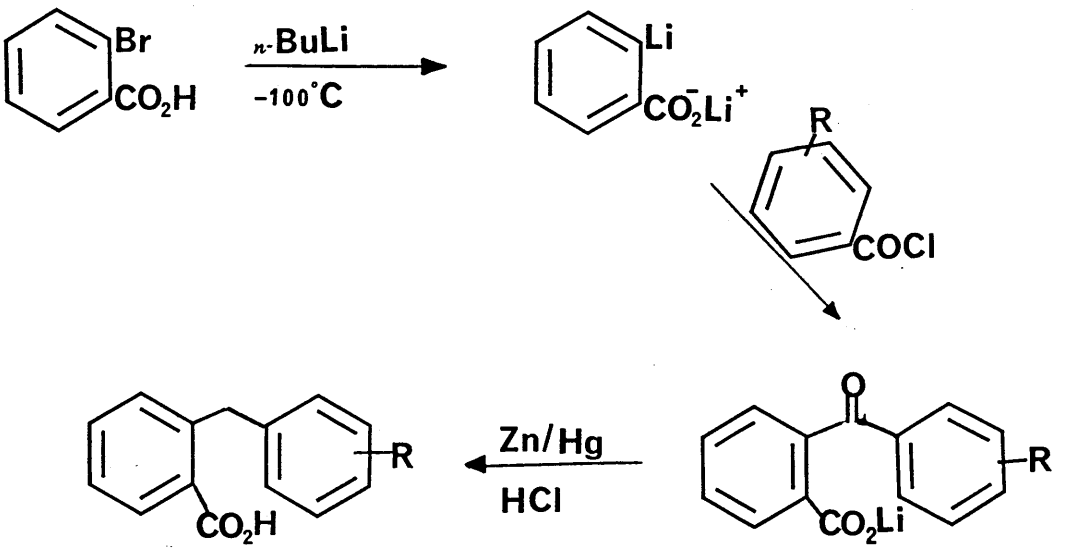
A second method for the preparation of benzylbenzoic acids involved the Friedel-Crafts condensation of a phthalic anhydride with an aromatic nucleus followed by a Clemmensen reduction of the keto group to give the corresponding benzylbenzoic acid. With this method however, it becomes very difficult to control the position of the substituent group. For example, the condensation of toluene and phthalic anhydride involves an electrophilic attack which can take place at the positions ortho and para to the methyl group with virtually no meta attack. Hence, not only does this route give a mixture of products, but the desired product may only be present to a small extent. Consequently this route was used only for the preparation of the parent compound, 2-benzylbenzoic acid.

Recently a new synthetic route has been devised for the preparation of benzoylbenzoic acids.[5] This involves the lithiation of o-bromobenzonitrile at -100°C followed by the addition of an alkyl benzoate (Scheme 3.5).



Scheme 3.5

This produces a benzoyl benzonitrile which when treated with hydrochloric acid gives the corresponding benzoylbenzoic acid. More recently this method has been modified by Parham et al.[6] Instead of a nitrile, 2-bromobenzoic acid is lithiated at -100°C in THF and to this is added a benzoyl chloride (Scheme 3.6).



Scheme 3.6

Provided that the temperature during addition is maintained at -100°C, the product is a benzoylbenzoic acid. This method was investigated and whilst it was successful the yields were often poor, secondly the substituted benzoic acids are rarely available commercially. Furthermore it is a very expensive route compared to that of Weizmann.[1]

3.2 Mechanism for the Cyclisation of Benzoylbenzoic Acids

During the initial stages of the project the system under investigation was that based on 2-naphthoylbenzoic acid. Cyclisation of 2-naphthoyl benzoic acid was carried out in sulphuric acid and the rate of cyclodehydration followed using ultraviolet spectrophotometry. Kinetic measurements were made at 25°C, monitoring the reaction at a wavelength of 453nm (maximum absorbence of 2-naphthoylbenzoic acid) using the method outlined for benzylbenzoic acids. Only one product was obtained from this cyclodehydration namely 1,2-benzanthraquinone. The identity of the product was confirmed by a comparison with the ^{13}C nmr of pure 1,2-benzanthraquinone purchased from the Aldrich Chemical Company, both ^{13}C nmr's were found to be the same. The reaction was found to be first order with respect to 2-naphthoylbenzoic acid and a rate constant of $1.54 \times 10^{-3} s^{-1}$ was obtained for the cyclisation in 99% sulphuric acid. This compares with a value of $6.2 \times 10^{-7}\ S^{-1}$ (extrapolated to similar conditions)[7] for benzoylbenzoic acid. From this a partial rate factor of 5000 is obtained for the 1 position in naphthalene. This should be compared to a value of about one obtained by Baddeley and Voss for the benzoylation of benzene and naphthalene using aluminium bromide,[8a] although Goldfarb et al.[8b] obtained a value of greater than one for the acetylation of benzene and naphthalene using acetyl chloride with stannic chloride catalyst in chlorobenzene. Partial rate factors for naphthalene involving other electrophilic aromatic

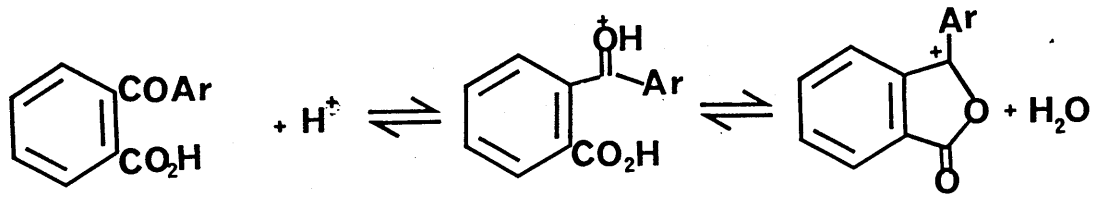
substitutions are reproduced in Table 3.21 below.

Table 3.21 Partial rate factors for electrophilic substitution of Naphthalene

Reaction	Partial rate factor	Ref.
Hydrogen exchange	1700	a
Alkylation	5	b
Sulphonation	200	c
Chlorination	1.3×10^5	d
Bromination	2×10^5	e
Mercuration	18	f

(a) C. Eaborn et al., J. Chem. Soc. (B), 1112 (1968)
(b) N.N. Lebender, J. Gen. Chem. USSR, 27, 2520 (1957)
(c) H. Cerfontain and A. Telder, Rec. Trav. Chim, 86, 527 (1967)
(d) S.F. Mason, J. Chem. Soc., 1233 (1959)
(e) S.F. Mason, J. Chem. Soc., 4329 (1958)
(f) G.A. Olah, S.H. Yu and D.G. Parker, J. Org. Chem., 41, 1983 (1976)

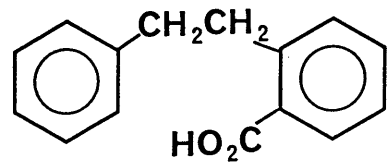
Although at first this seemed a reasonable system to use to investigate the kinetics and mechanism of cyclodehydration, major problems were encountered which eventually resulted in its replacement. Firstly the work of Noyce and Kittle[9] showed that benzoylbenzoic acids did not behave as ideal Hammett bases, the ketonic oxygen was being protonated and a slope of 0.67 was found for Log I against H_o. This system suffers similar drawbacks. Secondly protonation of benzoylbenzoic acids followed by loss of water leads to the formation of a lactol carbonium ion intermediate (Scheme 3.21).



Scheme 3.21

This mechanistic complication would also be present in the naphthoylbenzoic acid system. Thirdly the synthesis of substituted 2-naphthoylbenzoic acids would be very difficult and costly owing to lack of commercially available 2-bromonaphthalene derivatives, a key intermediate in the synthetic route to substituted naphthoylbenzoic acids.

As a result of this, an alternative system was sought and this resulted in the synthesis of 2-phenethylbenzoic acid (B).



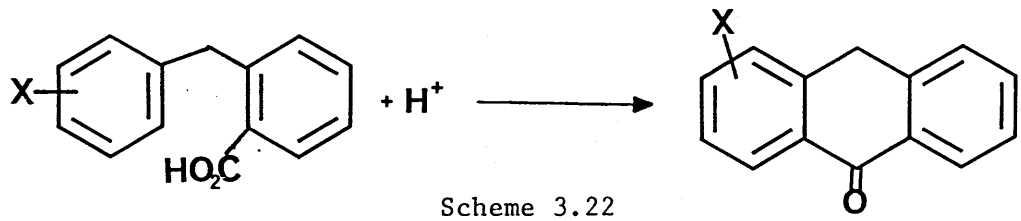
B

Unlike the cyclisation of 2-naphthoylbenzoic acid which produced benzanthraquinone, 2-phenethylbenzoic acid should result in the formation of a seven membered ring. A number of attempts to cyclise 2-phenethylbenzoic acid in sulphuric acid media (80-100%) were made, but all to no avail. Analysis of the products revealed that

cyclisation had not taken place, but instead the more reactive benzene ring had been sulphonated. It seems plausible to suggest that in this case the formation of a seven membered ring disfavours cyclisation because the transition state involves a greater loss of entropy than in the corresponding six membered ring case. Clearly in this case the rate of sulphonation was faster than that of cyclisation. At lower acid strengths both cyclodehydration and sulphonation were slow and only starting material could be recovered.

A much more fruitful system was that based on benzylbenzoic acid. In this system, since the keto group has been reduced, there is no chance of forming the lactol carbonium ion and furthermore the reactivity of the system towards intramolecular electrophilic substitution is increased.

In order to elucidate the mechanism of cyclisation of 2-benzylbenzoic acids in strong acid media (Scheme 3.22) the rates of cyclisations of a number of substituted benzylbenzoic acids were measured using ultraviolet spectrophotometry.



Scheme 3.22

Initially the cyclisations were carried out in sulphuric acid. Unfortunately sulphuric acid proved to be an unsuitable medium since good first order plots could not be obtained for the cyclisation of 2-benzylbenzoic acid. Cyclisation was taking place, but an isobestic point was not obtained. Examination of the products of cyclisation revealed that oxidation of the benzylic group was occurring after

cyclisation and the end result was the formation of an anthraquinone rather than an anthrone. This oxidation has been documented.[10,11,12]

Despite these complications it was possible to obtain rate constants for the cyclodehydration in sulphuric acid providing the acid strength was not too high. Again the rate of cyclisation was followed using ultraviolet spectrophotometry by observing the formation of product at 349nm at 25°C. A comparison of these rate constants with those for other cyclodehydration reactions is given in Table 3.22.

Table 3.22 Rate constants for cyclodehydration reactions in sulphuric acid

Compound	% Sulphuric Acid	Temperature °C	Rate Constant k/s^{-1}
2-benzylbenzoic acid	83.31	25	5.14×10^{-3}
2-naphthoylbenzoic acid	99.00	25	1.54×10^{-3}
2-benzoylbenzoic acid	84.54	25	2.7×10^{-9} (a)
2,2'-diphenic acid	83.00	60	3.3×10^{-6} (b)

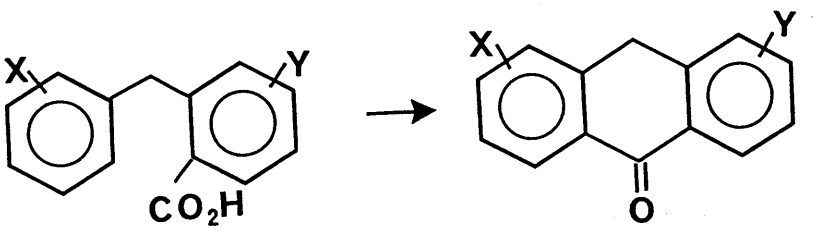
(a) - M.I. Vinnik et al., Rus. J. of Chem. 33, 253 (1959)
(b) - D.M. March and T. Henshall, J. Phys. Chem. 66, 840 (1962)

The rate constant has been obtained from Fig.4, but no units are available.

As can be seen from this table the results are as expected with 2-benzylbenzoic acid being the most reactive towards intramolecular

electrophilic substitution. Clearly the substitution of a CH_2 linkage instead of a C=O linkage activates the system both for protonation of the carboxylic acid group and towards electrophilic substitution by the aromatic group. The mechanistic details of the last two entries have been dealt with in section 7 of the Introduction, and it is likely that 2-naphthoylbenzoic acid reacts via the mechanism proposed for 2-benzoylbenzoic acid. The mechanism for the cyclodehydration of 2-benzylbenzoic acid will be discussed in later sections.

It is interesting to try and make a comparison between the rates of cyclodehydration of the benzylbenzoic acid and the benzoylbenzoic acid systems. Hammett ρ values have been determined for the cyclisation of benzylbenzoic acid with substituents in each ring in methanesulphonic acid (see later), (Scheme 3.23).



Scheme 3.23

Thus it should be possible to estimate quantitatively the effect of replacing a CH_2 by a C=O. First dealing with the effect of the presence of a C=O group on the equilibrium concentration of the corresponding carboxonium ion. The ρ value for this process was found to be -2.92 and the change in σ^+ on going from a CH_2 (-0.256) to a C=O (0.567) group will be 0.823 leading to a rate decrease of a factor of 253. This can now be compared with the effect of the presence of the C=O group on the reactivity of the benzene ring towards electrophilic aromatic substitution. The ρ value for this process was found to be

-5.3. Again a change in σ^+ of 0.823 leads to a rate decrease by a factor of 2.3×10^4. Thus overall there should be a rate decrease of 5×10^6. Despite the many assumptions involved in the calculation the result agrees very well with the observed decrease 2×10^6 indicating a similar mechanism for the two cyclodehydrations.

The first three compounds in Table 3.22 react to form a six membered ring and therefore the rate constants can be regarded as a measure of the relative ease of formation of the electrophilic species and its reactivity towards the aromatic moiety. For 2,2'-diphenic acid, however, reaction leads to the formation of a five membered ring and hence the relative size of the rate constant also reflects the ease of formation of a five membered ring compared to the six membered ring. Unfortunately the units of this rate constant are unknown but they are likely to be min^{-1} and therefore any comparison made will be based on this assumption. The rate constant recorded was measured at 60°C, however, a value can be extrapolated using the activation energy of about 120 KJ mol^{-1} given in the paper. A rate constant of 1.65×10^{-8} s^{-1} is obtained at 25°C, a factor of 3×10^5 slower than benzylbenzoic acid. To make a comparison of 5 and 6 membered ring formation it is necessary to compensate for the effect of conjugation between the two rings and the presence of two carboxylic acid groups. Using the ρ values obtained later the presence of a -COOH group on the reactivity of the benzene ring towards electrophilic aromatic substitution should reduce the rate by a factor of 50. The loss of a CH_2 linkage and conjugation with a -Ph-COOH should result in a further reduction in rate both in terms of the electrophilicity of the aromatic moiety and the extent of carboxonium ion formation (σ^+ for Ph- = -0.21, σ^+ for $-CH_2Ph$ = -0.27). However, it is doubtful whether this could be sufficient to reduce the rate by a factor of 10^4. The fact that the

2,2'-diphenic acid is so much slower indicates that the five membered ring cyclisation is inherently slower than the six membered ring formation. This is in contrast to the work of Mandolini[13,14] who showed that, as indicated in Table 3.23, the rate of cyclisation generally increases on going from seven to five membered rings.

Table 3.23 Relative rates of ring closure for the reaction $Br(CH_2)_{n-2}CO_2^- \longrightarrow (CH_2)_{n-2}C(=O)O$

Ring Size	Relative rate
5	1.5×10^6
6	1.7×10^4
7	97.0

The reduction in rate on forming a five membered ring in this instance probably arises as a result of steric interaction between the other COOH group and the phenyl ring in the planar transition state.

In response to the problems relating to sulphuric acid another acid medium was employed. Polyphosphoric acid was chosen because of the lack of possible side reactions, such as oxidation, and the fact that it is a popular reagent for Friedel-Crafts type cyclisations, and consequently a good deal of reliable data would be available in the literature. A number of mixtures of polyphosphoric acid were prepared from phosphorous pentoxide and water and their concentrations determined using refractive index measurements, (see experimental section).

Cyclisation of 2-benzylbenzoic acid was carried out at 40°C and kinetic measurements were made using ultraviolet spectroscopy at 346nm (max. absorbence of anthrone). The reaction was found to be first order with respect to 2-benzylbenzoic acid as confirmed by the good fit obtained using the least squares method. The rate constant thus obtained is given below in Table 3.24 which also includes kinetic data on similar cyclisation in PPA[15].

Table 3.24 Some Rate Constants for Cyclodehydration Reactions in Polyphosphoric Acid

Compound	$\%P_2O_5$	Temperature °C	Rate Constant, ks^{-1}
2-benzylbenzoic acid	81.5	40	1.67×10^{-3}
2-benzoylbenzoic acid	81.6[a]	80	1.36×10^{-4}
2-(4-chlorobenzoyl) benzoic acid	81.6[a]	80	1.36×10^{-6}
2-(4-toluoyl) benzoic acid	81.6[a]	80	2.89×10^{-5}
2-phenoxy benzoic acid	83.05[a]	44	2.22×10^{-4}

a - These values represent wt.% phosphorous pentoxide.

In all cases a six membered ring is formed on cyclisation and the table indicates that at the same temperature the rate of cyclisation of 2-benzylbenzoic acid is a good deal faster than the rates for benzoyl-benzoic acids. These results are as we would expect from a consideration of the substituent effects. In the case of benzyl-benzoic acid the ring is activated towards electrophilic substitution

by the presence of the methylene group. With 2-phenoxybenzoic acid this activation is even greater due to oxygen linking the two rings. The rate constant for this compound, however, is much lower than expected.

Although polyphosphoric acid appeared to be a good reagent for these cyclodehydrations in that it gave rise to no side reactions there were other problems encountered with this medium. These were mainly concerned with the high viscosity of polyphosphoric acid. It proved to be very difficult if not impossible to carry out the cyclisation in a homogeneous mixture. Even at high temperatures the viscosity of the medium was far too high such that only in dilute solutions (eg <60%) was the viscosity acceptable for kinetic measurements; unfortunately these acidities were far too low to effect cyclisation.

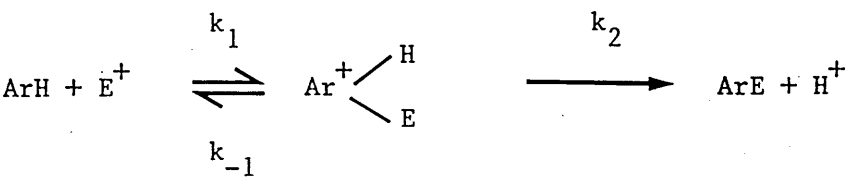
Trifluoroacetic acid was also employed to cyclise benzylbenzoic acid, but the acidity of the medium was too low for cyclisation to take place. Ultimately methanesulphonic acid was employed and, although this was a weaker acid than sulphuric acid, it proved to be a good reagent for cyclisations of benzylbenzoic acids. It did not suffer from as many drawbacks as other media. No oxidation or sulphonation was observed in this acid and it does not have a high viscosity. Furthermore most of the work could be carried out at 25°C. This medium was therefore employed in all further mechanistic studies, unless stated otherwise. Commercially purchased methanesulphonic acid (98%) was somewhat impure having a brown appearance, clearly in this form the acid is unsuitable for spectroscopic techniques. Methanesulphonic acid was vacuum distilled prior to use and different concentrations obtained by diluting the distilled acid (see experimental section) with distilled water.

Each substituted benzylbenzoic acid was cyclised in methanesulphonic acid of different acid strengths and the rate of reaction determined using ultraviolet spectrophotometry by observing the rate of formation of product. In all cases the rate of reaction was found to be first order with respect to the benzylbenzoic acid and an excellent correlation coefficient was obtained by the least squares method for each acid (usually 0.999 or 1.000). Duplicate runs did not differ by more than ±5%. An isobestic point was observed in all cases. Using this method the rate constant for each substituted benzylbenzoic acid was calculated and details of these results will be presented in the following pages. All work was carried out at 25°C ± 0.01 unless stated otherwise. Product studies, details of which will be given later, were also performed and in all cases no oxidation or sulphonation could be detected and only anthrones were obtained. Most of this work was carried out in the acidity range 90-100% wt./wt. methanesulphonic acid, although for two compounds this range was increased to 85-100%. On increasing the concentration of water not only did the reaction slow down as would be expected, but above a certain limit (about 10%) precipitation of the product was observed. This was only a problem for the two compounds which were studied as low as 85% methanesulphonic acid (Nos. XII and XIII). However, the amount of precipitation was very small (<10%). Nevertheless its effects could be clearly seen on the rate profiles obtained using the ultraviolet spectrophotometric method; towards the end of the reaction the absorbence of the product decreased gradually. This must be borne in mind when considering these results.

3.3 Deuterium Isotope Effect

Isotopic labelling is now a widely used method for the analysis of reaction mechanisms. Hydrogen isotope effects have been extensively studied for electrophilic aromatic substitutions, and numerous reviews of the subject are now available.[16,17]

In the traditional mechanism of electrophilic aromatic substitution no deuterium isotope effect should be observed. This is because the loss of hydrogen is not involved in the rate limiting step. For a large number of such reactions this has been found to be the case but isotope effects have been observed in a few electrophilic aromatic substitutions. Generally these effects are smaller than expected; k_H/k_D being about 1-3 rather than 6-7. These effects can be explained in terms of the reversible formation of a σ complex. Consider the reaction between an aromatic moiety and an electrophile (Scheme 3.31). A deuterium isotope effect can arise from this situation in one of two ways.



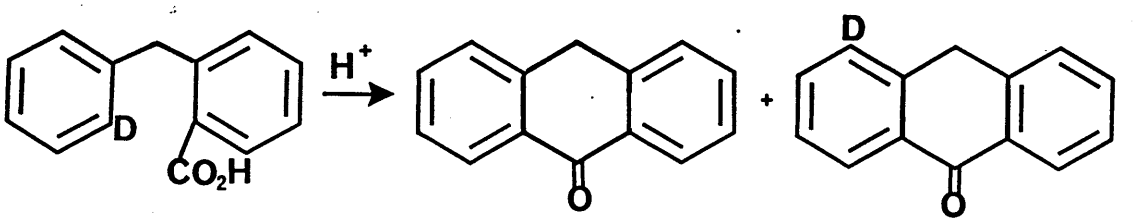
Scheme 3.31

For a situation where no isotope effect is found the second step will have a much larger rate, i.e. $k_2[Ar^+HE] > k_1\ [ArH]\ [E^+]$. If however, the second step has a similar or smaller rate than the first then an isotope effect would be observed; this situation is somewhat unusual for electrophilic aromatic substitutions, as the first step is

generally the slower one.

So far the reversibility of the first step has been ignored, but this is probably the cause of many of the small isotope effects observed. The rate at which Ar^+HE and Ar^+DE revert to ArH and ArD respectively should be the same as the Ar-H bond is not being broken. However, in the forward step where Ar^+DE and Ar^+HE give ArE a carbon hydrogen bond is broken and hence the latter should be faster. Where $k_2 >> k_{-1}$ no effect would be observed as most of the intermediates go to product and the reversible step becomes insignificant. If however, k_2 is similar to k_{-1} then k_2 for Ar^+DE is smaller than k_2 for Ar^+HE and k_{-1} is the same for both such that Ar^+DE gives much more starting material. Thus k_2/k_{-1} (partition factor) is smaller for Ar^+DE than for Ar^+HE. An isotope effect should thus be observed as ArD will react at an overall slower rate than ArH. This reversibility of the first step is often a result of steric hindrance and such a situation clearly arises in diazonium coupling reactions.[18] Another similar situation arises in the nitration of 1-methyl-2,4,6-tri t-butylbenzene. In this case a k_H/k_D value of 3.7 was observed.[19]

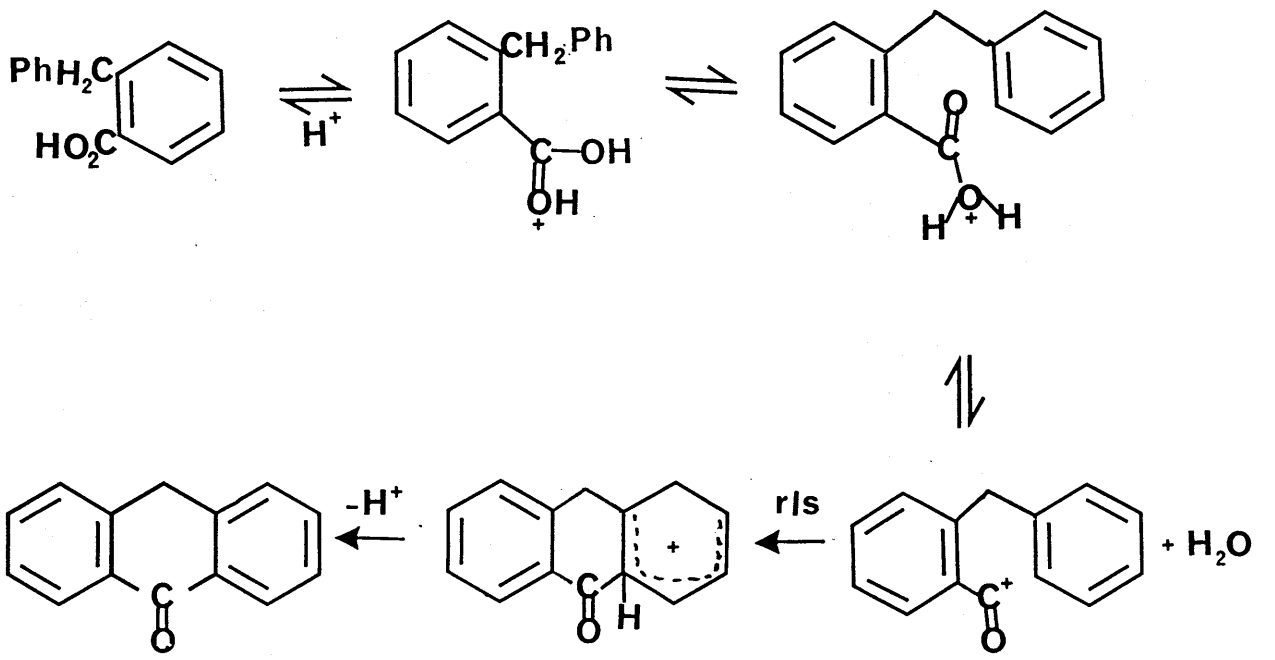
The methods of measuring isotope effects have already been discussed earlier and in this project both methods were used to show the lack of an isotope effect. Kinetic measurements were made on the cyclisation of 2(2-deuterobenzyl)benzoic acid in methanesulphonic acid, and the results compared with those of 2-benzylbenzoic acid in the same medium. The k_H/k_D value was found to be 1.04 and was constant over the range 92-100% methanesulphonic acid. Clearly the breaking of a C-H bond is not involved in the rate limiting step. This conclusion was confirmed using product studies carried out on 2(2-deuterobenzyl)benzoic acid (Scheme 3.32).



A B

Scheme 3.32

The two possible isomers were formed in about equal quantity, 49% of the deutero isomer B and 51% of the undeuterated isomer A. At this point a tentative approach can be made on formulating the reaction mechanism, by analogy with the mechanism of cyclisation of benzoylbenzoic acid, (Scheme 3.33).



Scheme 3.33

In this scheme initial protonation of the benzoic acid occurs on the carbonyl group, but if protonation occurs on the OH group this can be followed by the loss of water and the formation of a carboxonium ion. This is followed by electrophilic substitution which is possibly rate limiting. The lack of an isotope effect indicates that the last step, loss of H^+, must be very much faster than the back reaction of the preceding step and therefore the reversible nature of the preceding step must be unimportant. (Work was also carried out to shed light on the initial steps in the mechanism and this will be discussed later.)[2]

These results are in contrast with those obtained from similar cyclodehydrations. For example, when 2-deutero-2'-carboxybiphenyl was cyclised in sulphuric acid an analysis of the reaction products indicated a k_H/k_D value of 1.31.[20] This clearly shows the presence of an isotope effect.

A cyclodehydration reaction closely resembling the one in this project is that of 2-benzoylbenzoic acid. Extensive work has been carried out on this system and isotopic data is also available.[21] The results show a variable isotope effect for the rate of cyclisation, in 97.13% sulphuric acid a k_H/k_D value of 1.29 was obtained whereas in 100.3% sulphuric acid this figure fell to 1.10. After correction for the fraction of deuterium remaining in the product, the isotope effect was found to be fairly constant at 1.46. Although at first sight this small figure seems to indicate a secondary isotope effect (usually in the region 1-1.7), on close examination of the data the authors claim that this figure was the result of a primary isotope effect,[21] although this would be expected to be much larger (1-18). Hence, the decomposition of the σ-complex is claimed to be partially rate limiting in contrast to the corresponding σ-complex obtained from

benzylbenzoic acids. It seems strange that an isotope effect should be observed in the case of the benzoylbenzoic acid but not the benzylbenzoic acid. The replacement of a CH_2 linkage by a C=O should make the corresponding carboxonium ion less stable, this means the breakdown of the Wheland intermediate to the electrophile and aromatic should be less likely. This contrasts with the observation of an isotope effect which indicates this step should become more reversible.

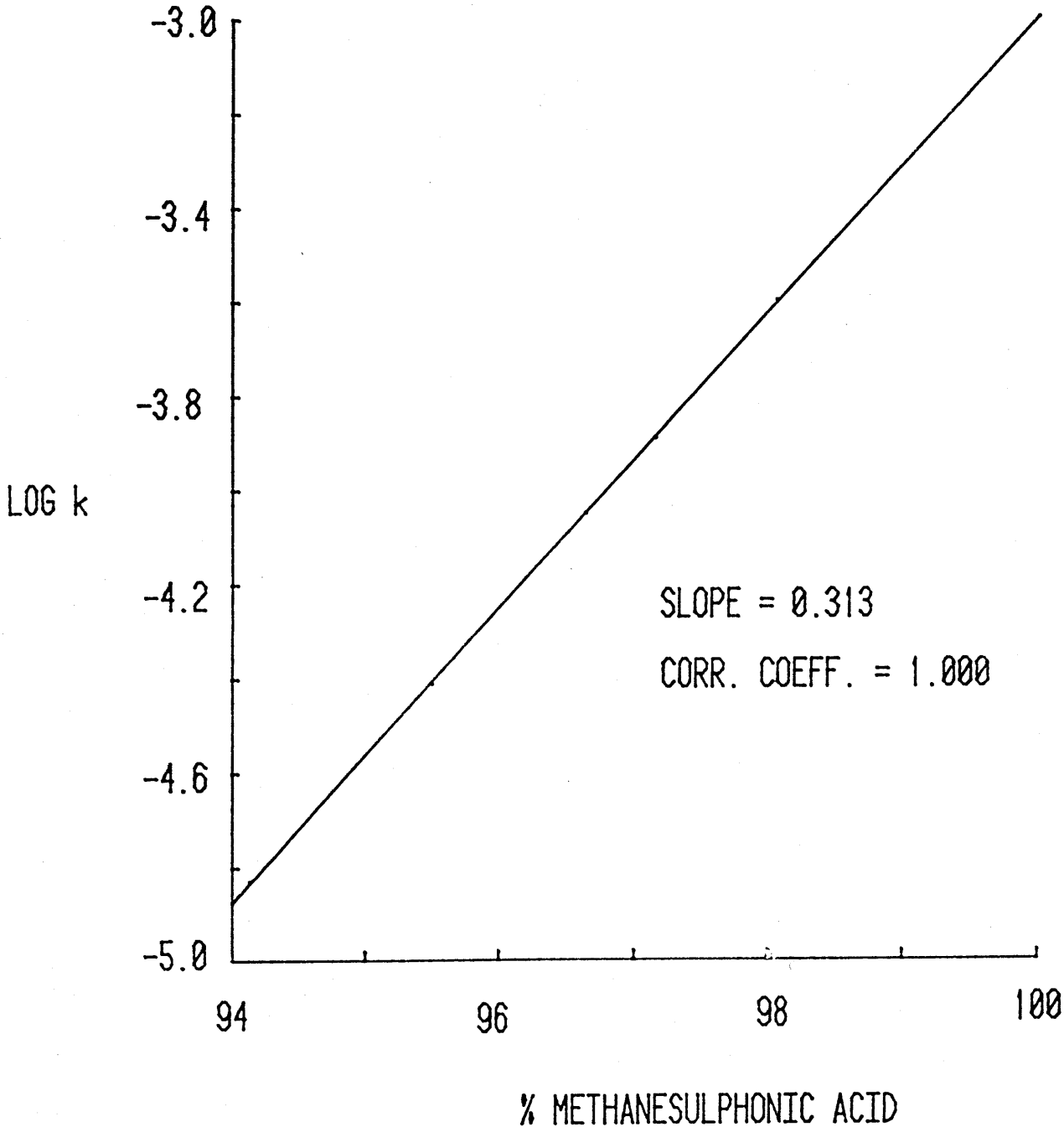
3.4 Mechanism for the Cyclodehydration of Benzylbenzoic Acids

In order to examine the influence of methanesulphonic acid on the cyclisation process the log of the rate constant (log k) was plotted in the first instance against the w/w % acidity of methanesulphonic acid. As can be seen from the following pages in all cases a reasonable linear correlation was obtained with gradients of less than unity. Despite the w/w % not being a particularly informative measure of acidity, certain observations can be made from these plots (see Table 3.41 where the data is presented in terms of measured decreasing reactivity), the main one being that the presence of a deactivating group, such as Cl or F, in the benzyl ring leads to a sharp increase in the gradient. For example with a 3-methyl group in the benzyl ring a slope of 0.237 (93.69% - 98.52%) was obtained but with a chloro group in the same position the slope was increased to 0.515 (95.86% - 99.01%). Further mechanistic interpretation of these slopes cannot be performed since w/w % is not a particularly informative measure of acidity. A much better scale of acid strength is the acidity function.

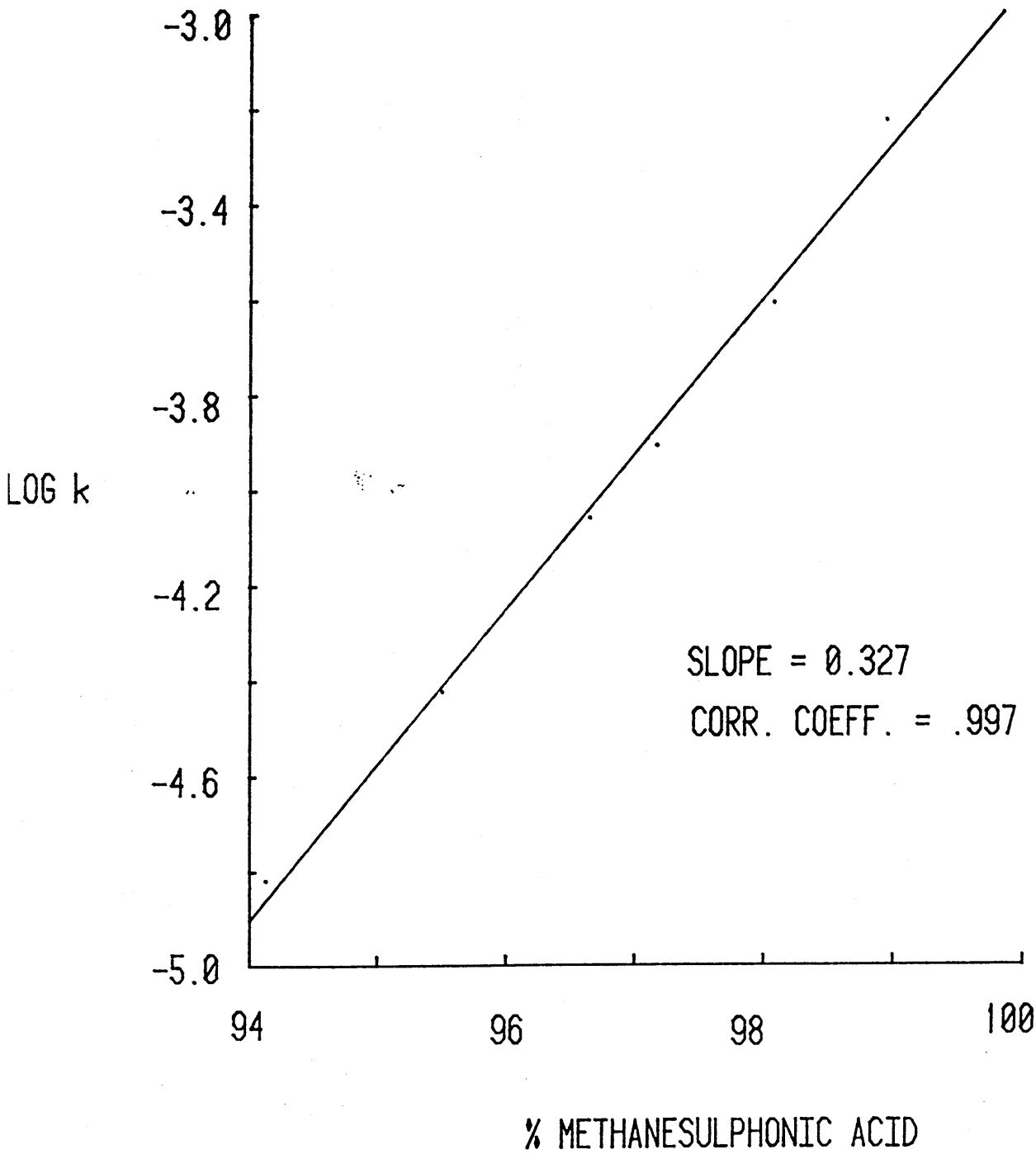
Table 3.41 Data on plots of log k vs % Methanesulphonic acid and log k (DiMeO cpd) for Benzylbenzoic acids

Compound	Slope/ % Acid	Corr. Coeff.	Slope/ log k-DiMeO	Corr. Coeff.	No. of points
2(3-Hydroxybenzyl)-benzoic acid	0.246	0.999	1.06	1.000	5
2(3-Methoxybenzyl)-benzoic acid	0.294	0.991	1.16	0.992	6
2(3-Tolyl)benzoic acid	0.237	0.997	1.13	0.997	6
2(4-Tolyl)benzoic acid	0.269	0.996	1.23	0.999	5
2(4-Methoxybenzyl)-benzoic acid	0.231	0.990	1.04	0.995	5
2(4-Hydroxybenzyl)-benzoic acid	0.267	0.991	1.07	0.995	5
2-Benzylbenzoic acid	0.313	1.000	1.16	0.992	6
2(3-Fluorobenzyl)-benzoic acid	0.406	0.995	1.79	0.999	5
2(3-Chlorobenzyl)-benzoic acid	0.515	0.998	1.95	0.999	4
2(4-Fluorobenzyl)-benzoic acid	0.463	0.998	1.96	0.998	4
2(4-Chlorobenzyl)-benzoic acid	0.713	0.999	2.98	0.999	4
2(3-Tolyl)-4,5-dimethoxy-benzoic acid	0.204	0.998	-	-	11
2(3-Tolyl)-4,5-dimethyl-benzoic acid	0.205	0.993	0.975	0.997	10
2(3-Tolyl)-4,5-diphenyl-benzoic acid	0.222	0.996	1.03	0.998	6
2(3-Tolyl)-4,5-dichloro-benzoic acid	0.242	0.997	0.997	0.995	4

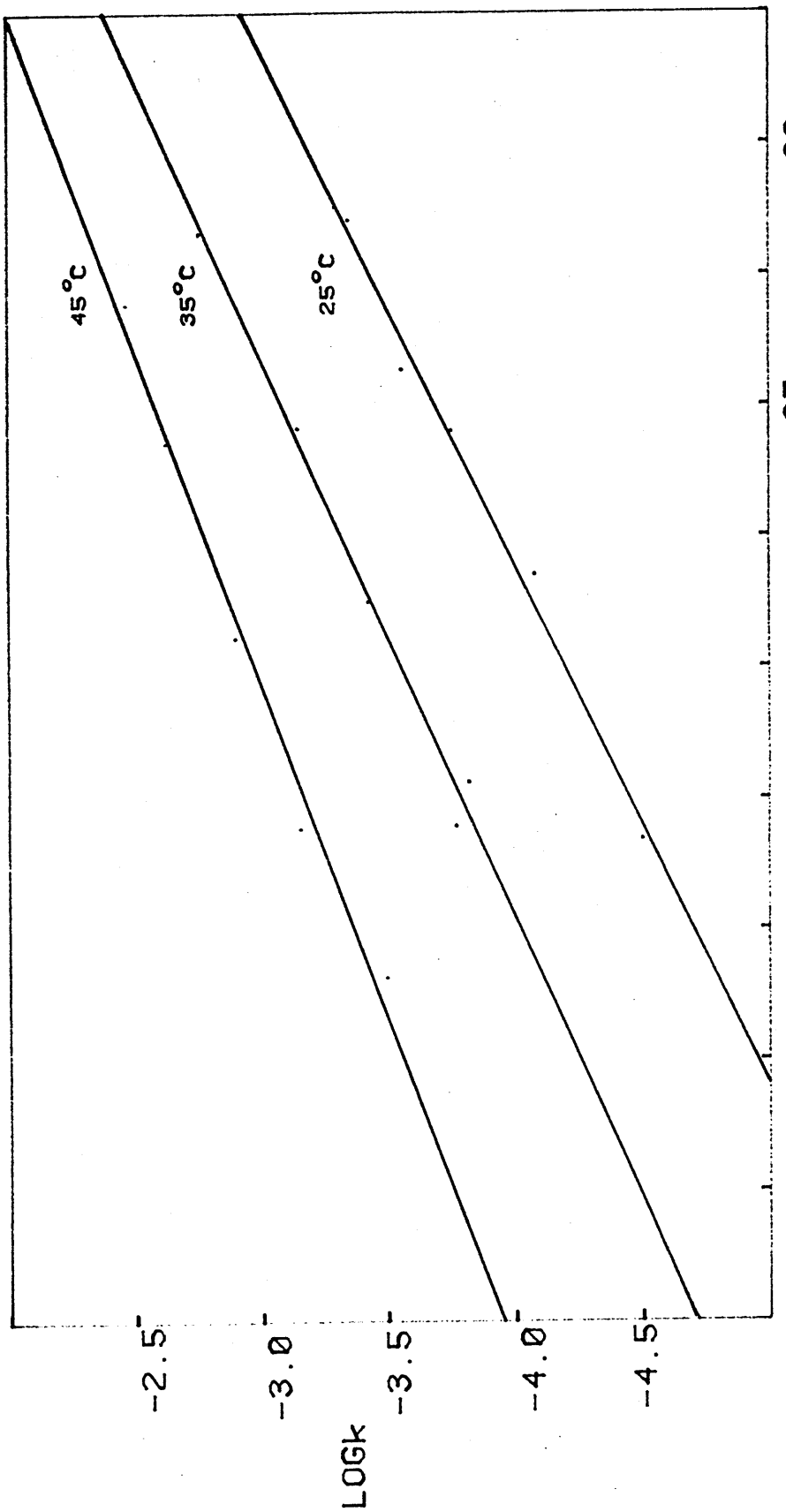
PLOT OF LOG k VS % $MeSO_3H$ ACID FOR 2-BENZYL BENZOIC ACID (1)



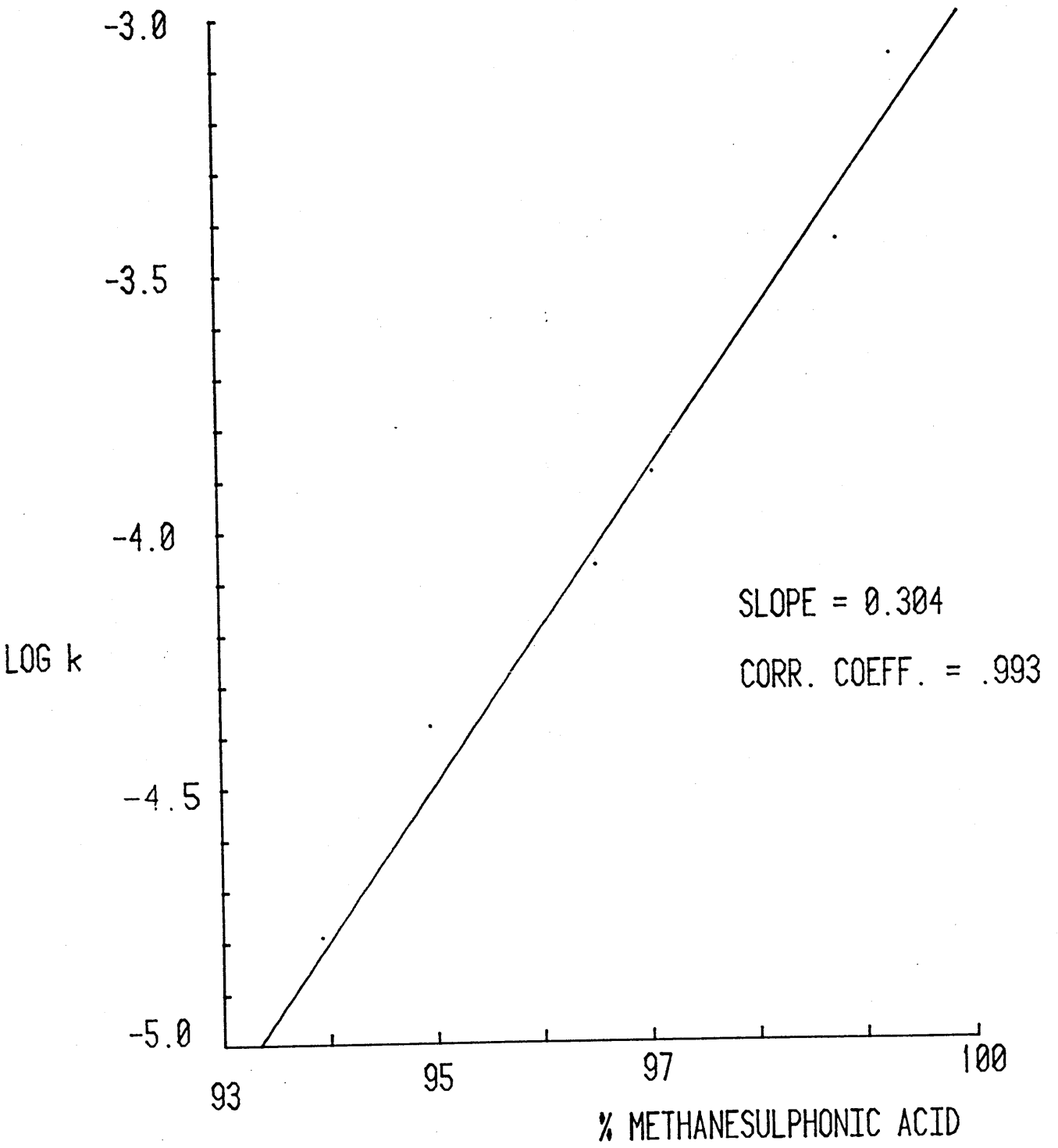
PLOT ØF LOG k VS % $MeSO_3H$ ACID FOR 2-D CPD (1a)



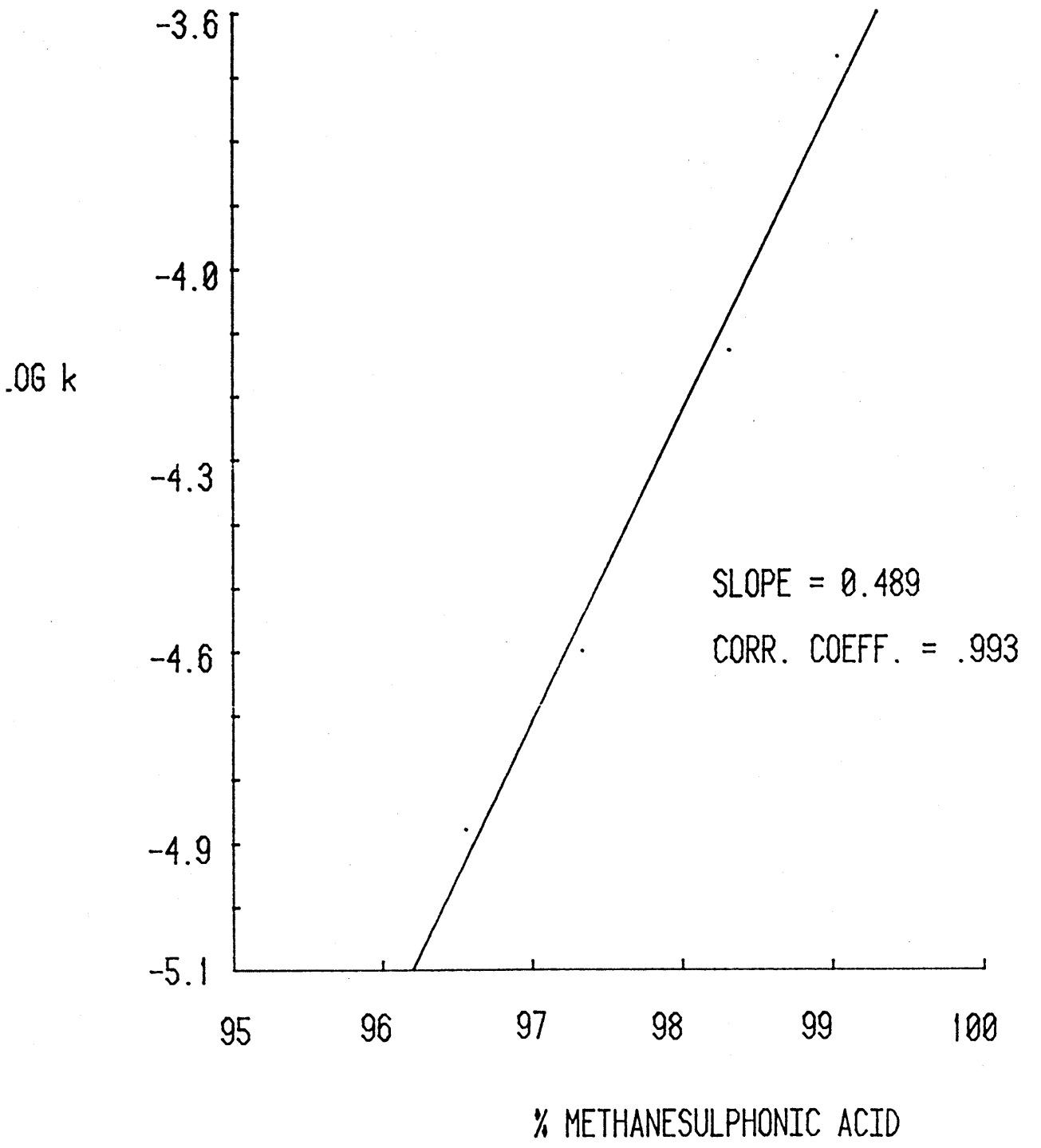
PLOT OF LOGk vs %$MeSO_3H$ FOR 3-Me CPD (II)



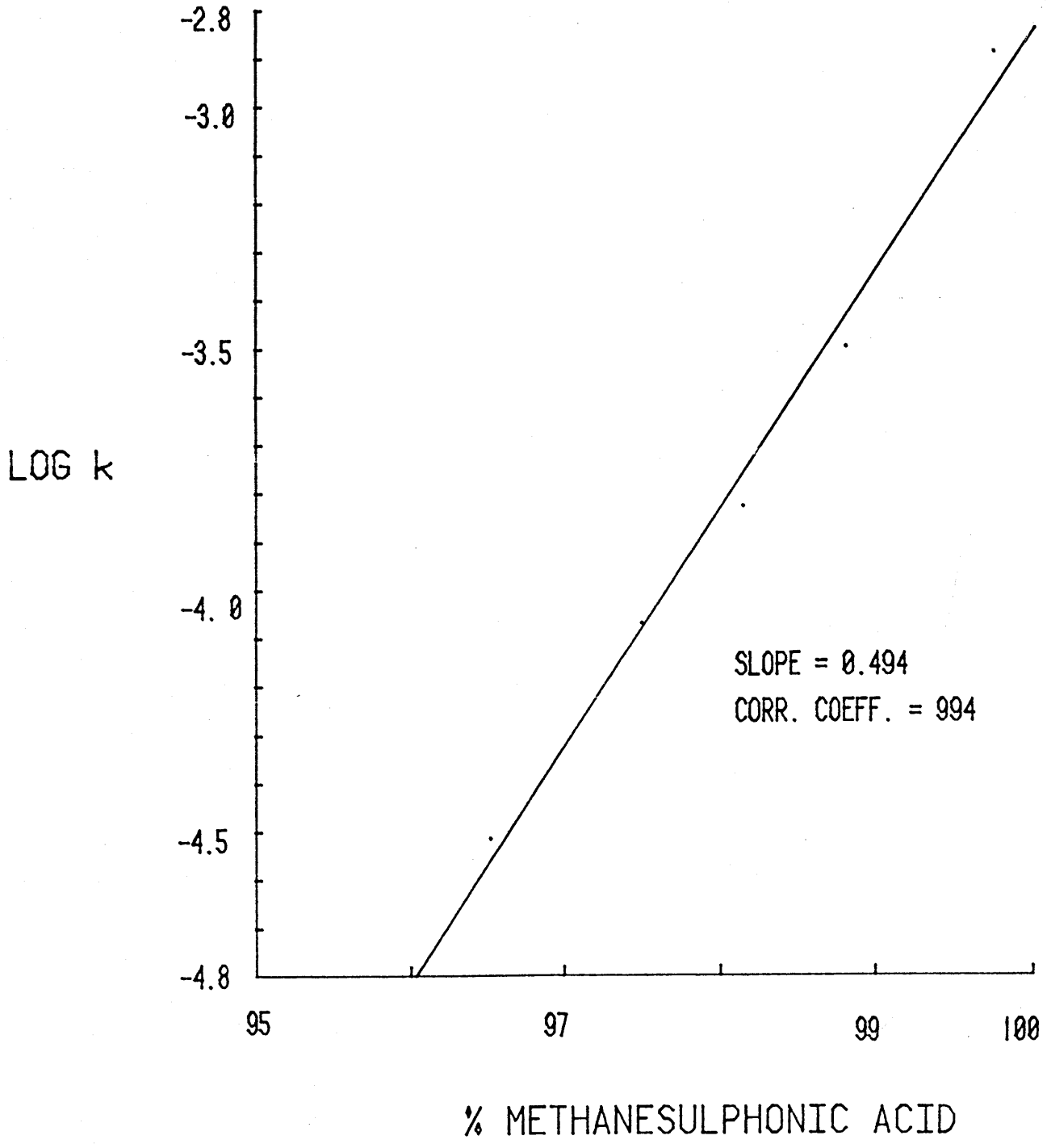
PLOT OF LOG k VS %$MeSO_3H$ ACID FOR 3-MeO CPD (III)



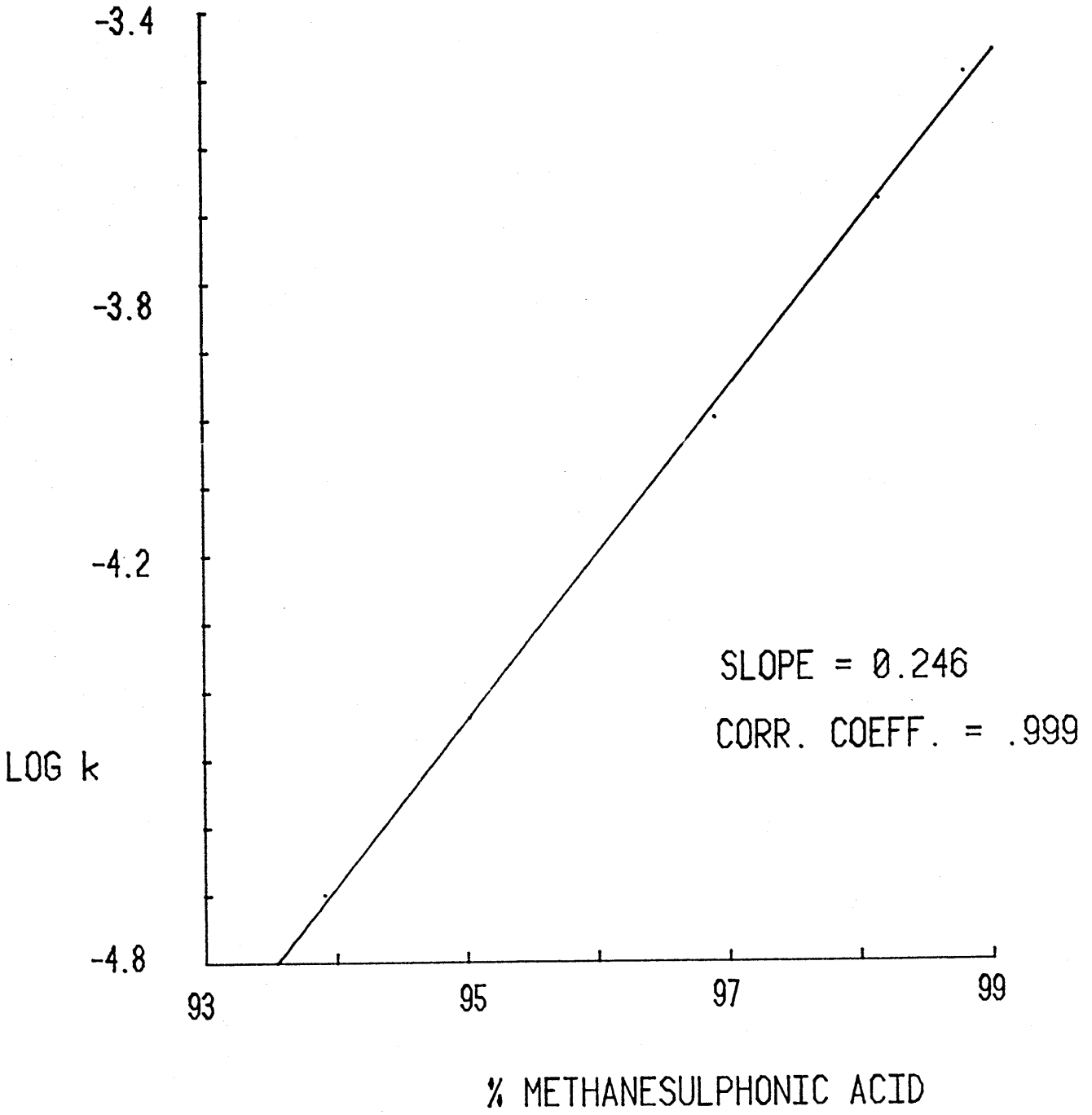
PLOT OF LOG k VS % $MeSO_3H$ FOR 3-Cl CPD (IV)



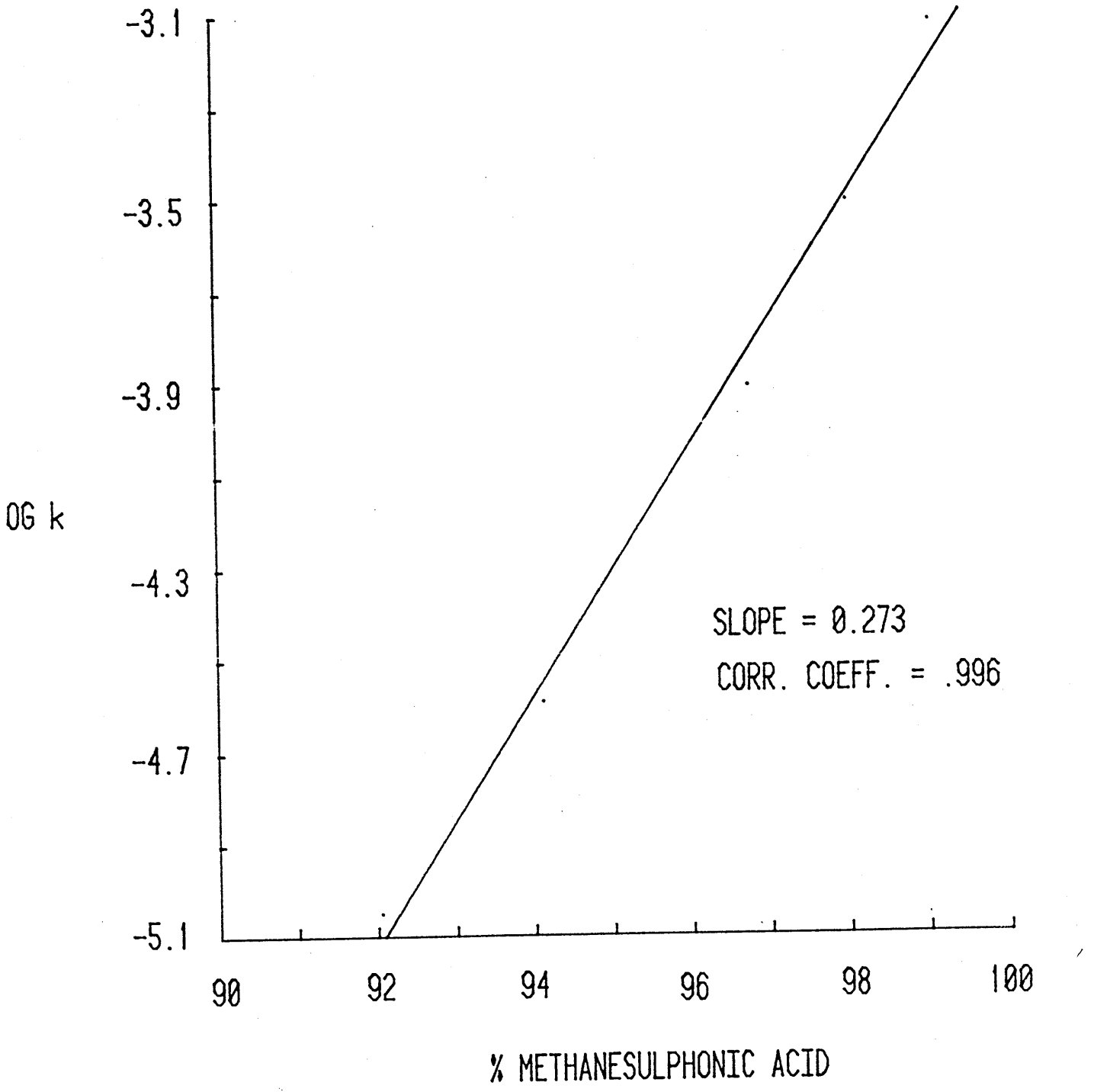
PLOT OF LOG k VS % $MeSO_3H$ FOR 3-F CPD



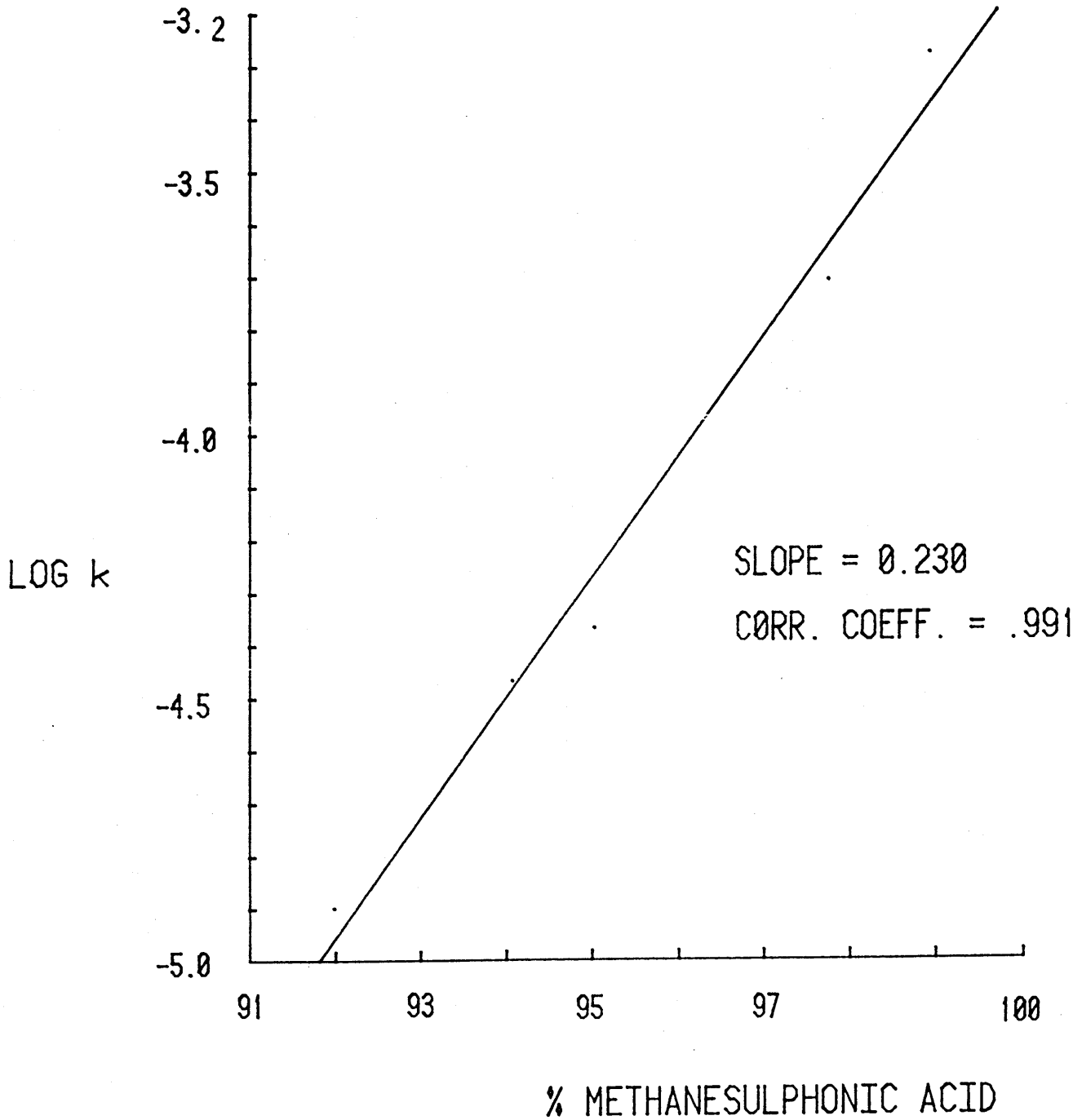
PLOT OF LOG k VS % $MeSO_3H$ FOR 3-OH CPD (VI)



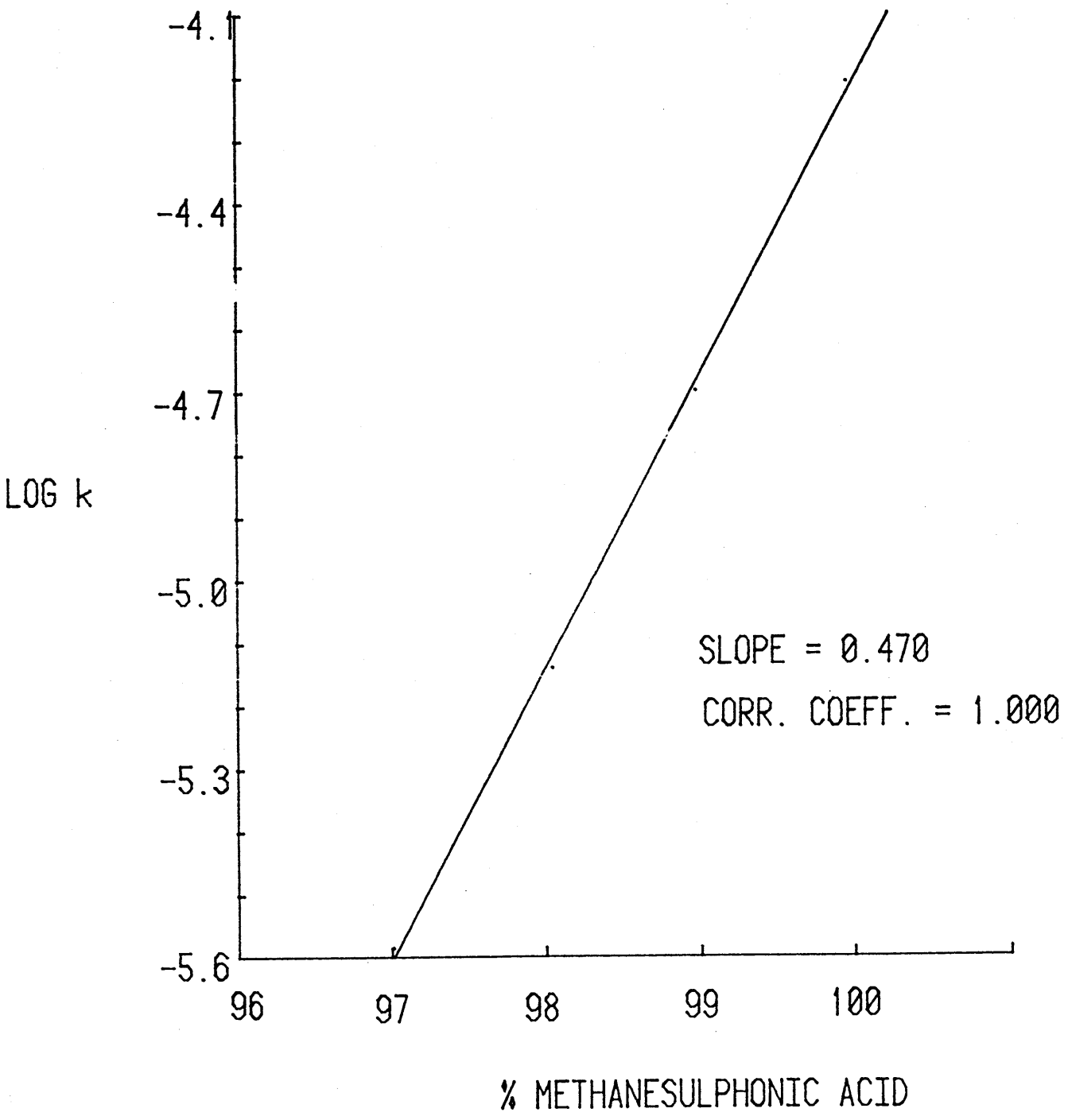
PLOT OF LOG k VS % $MeSO_3H$ ACID FOR 4-Me CPD (VII)



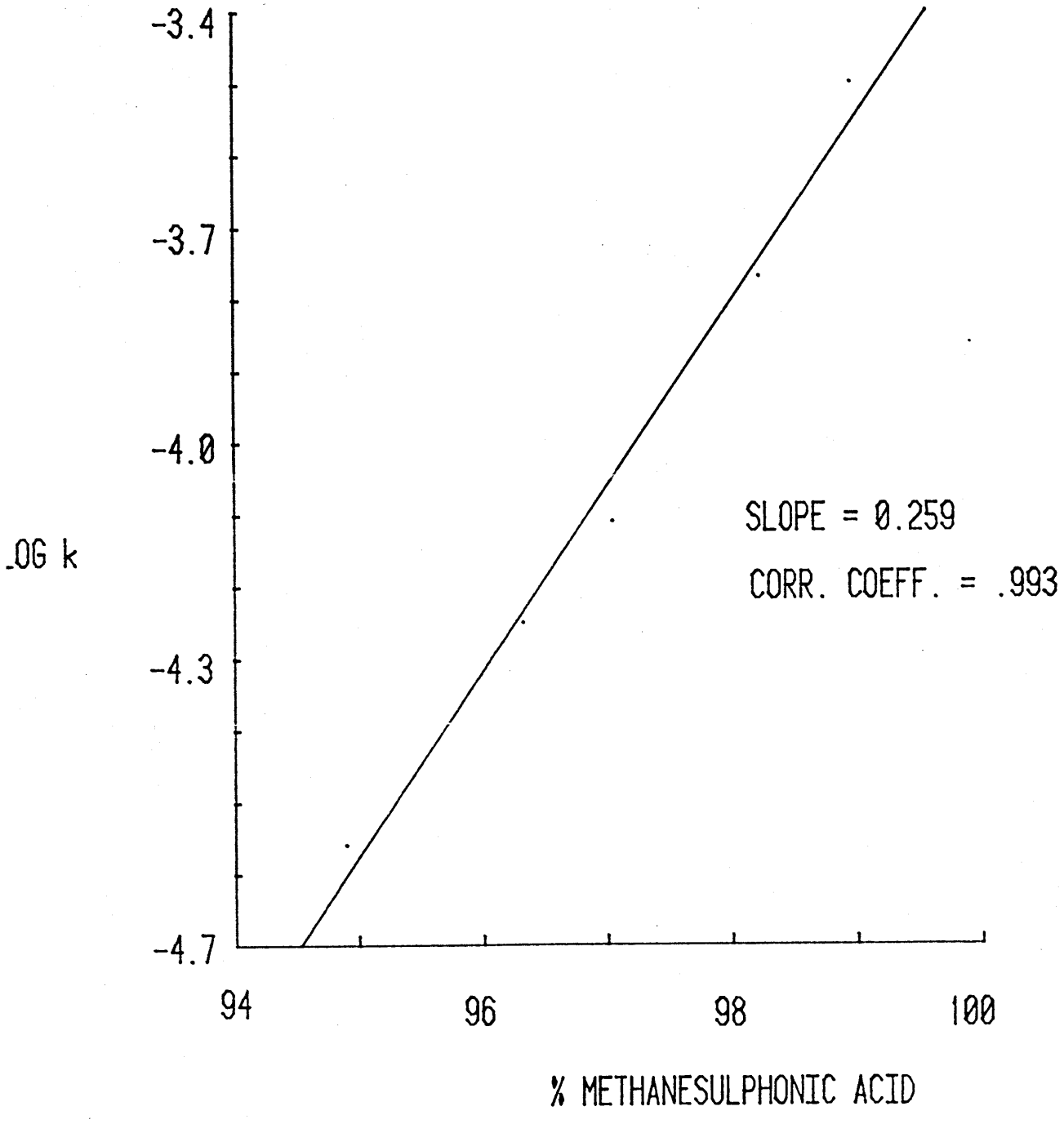
PLOT OF LOG k VS % $MeSO_3H$ FOR 4-MeO CPD (VIII)



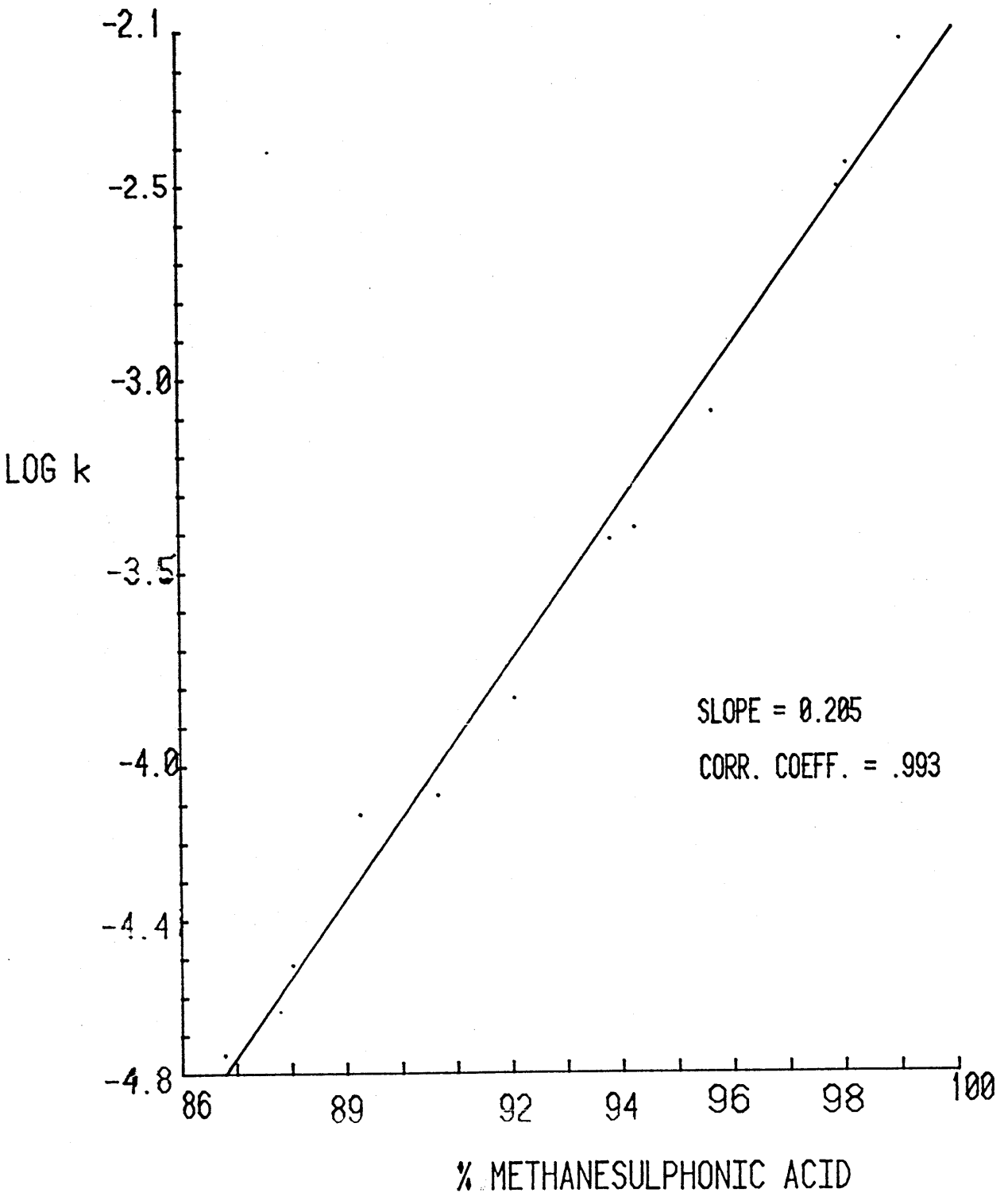
PLOT OF LOG k VS % $MeSO_3H$ FOR 4-F CPD (X)



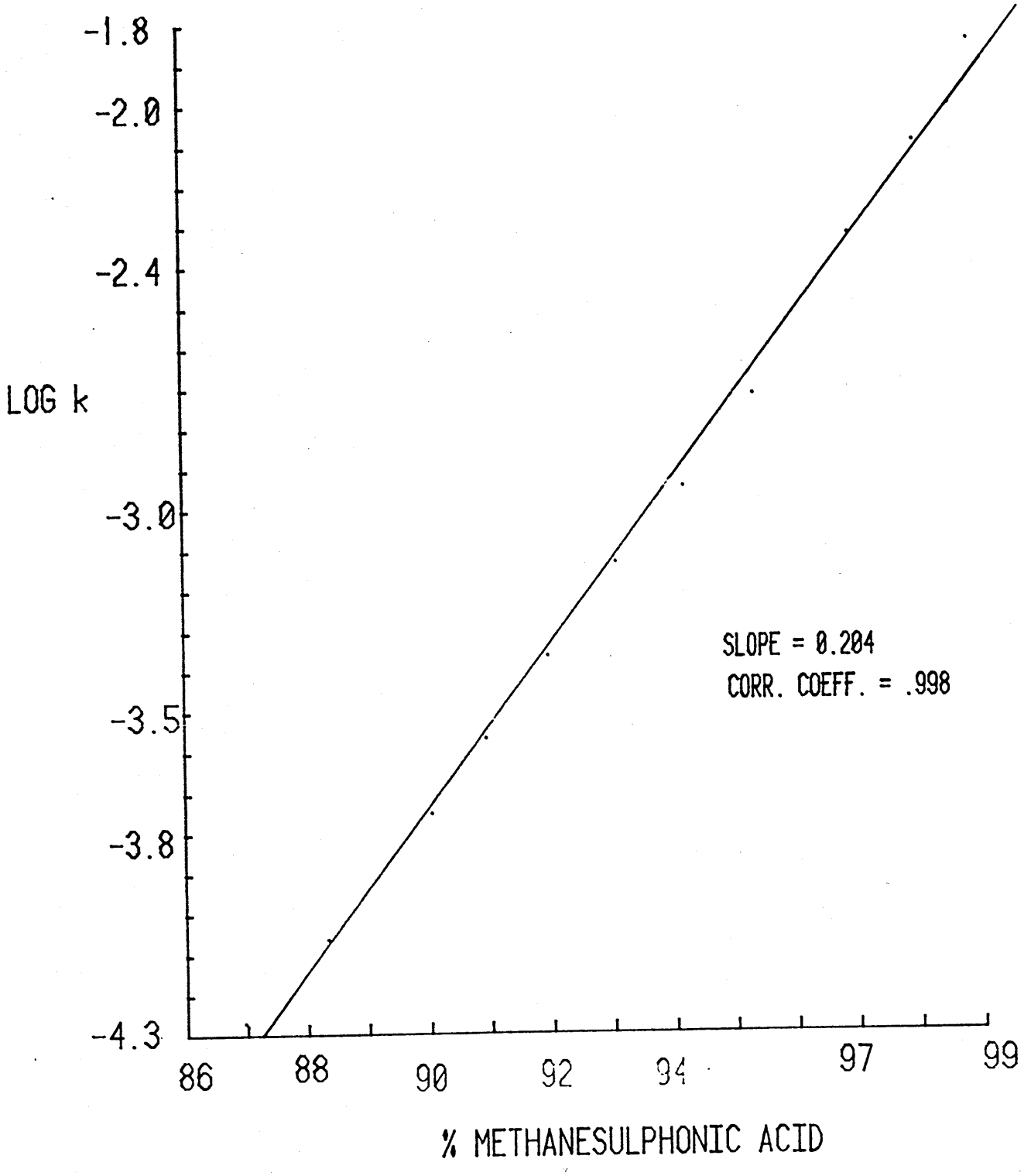
PLOT OF LOG k VS % $MeSO_3H$ FOR 4-OH CPD (XI)



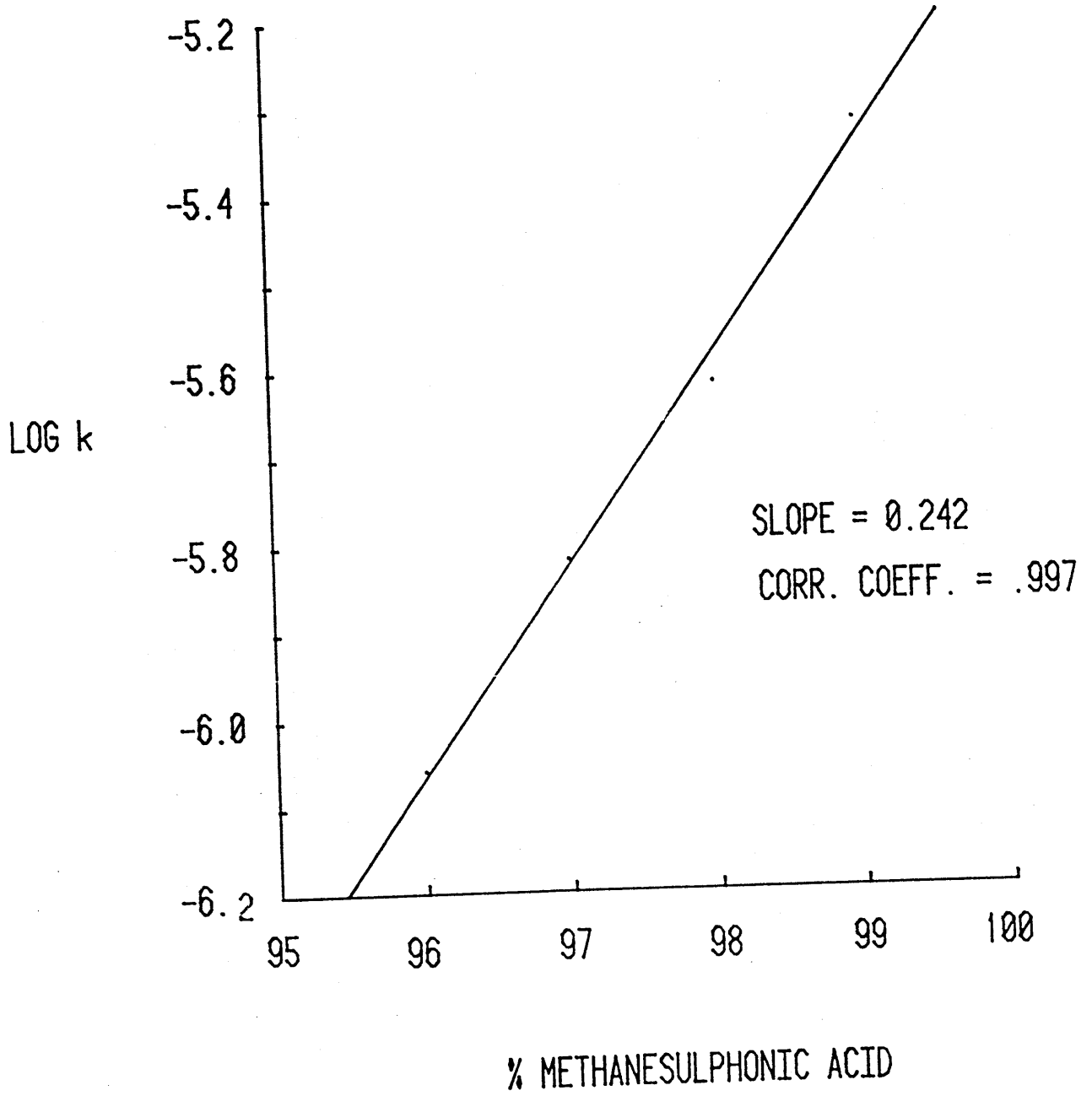
PLOT OF LOG k VS % $MeSO_3H$ FOR DIMe CPD (XII)



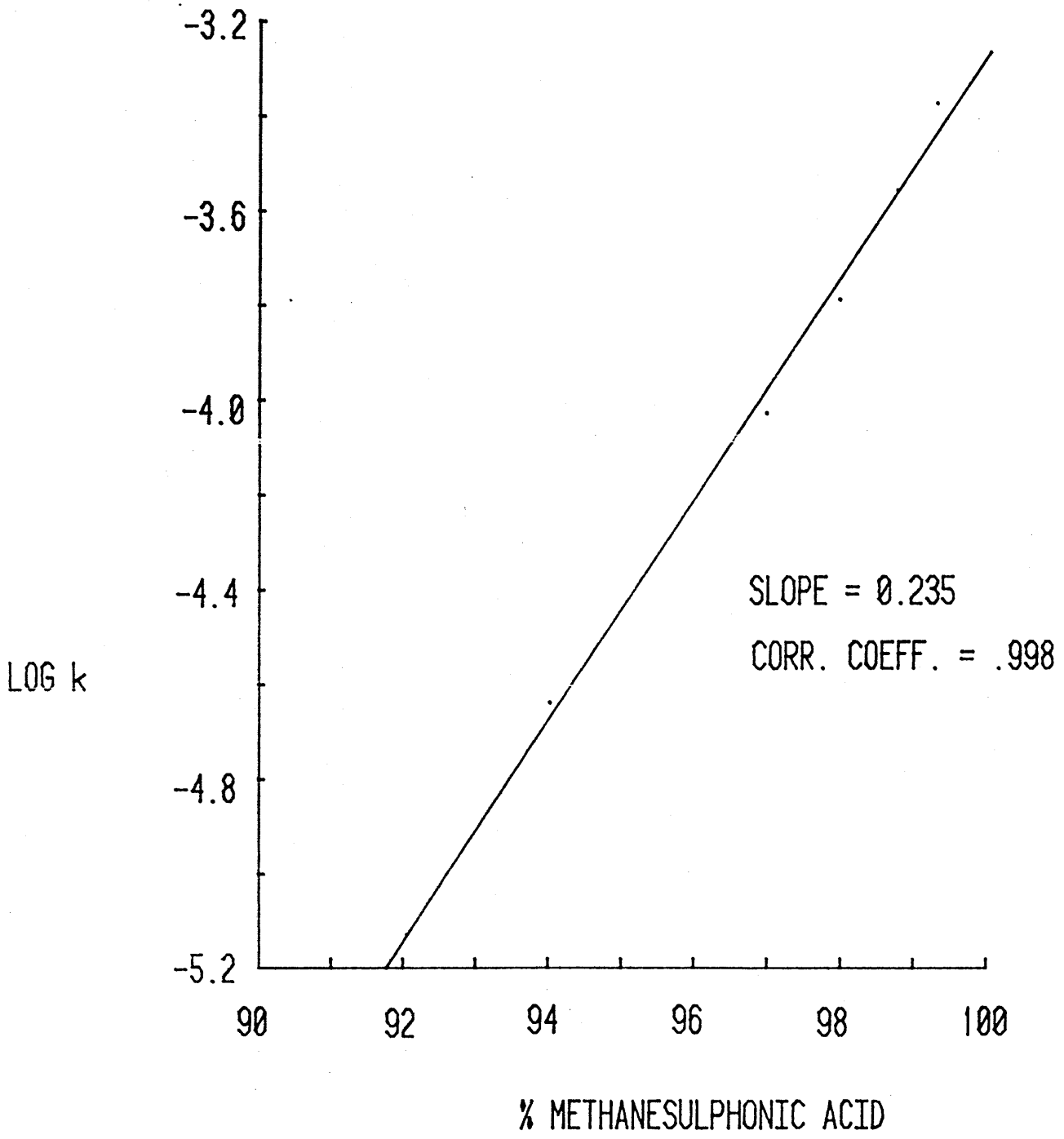
PLOT OF LOG k VS % $MeSO_3H$ FOR DIMeO CPD (XIII)



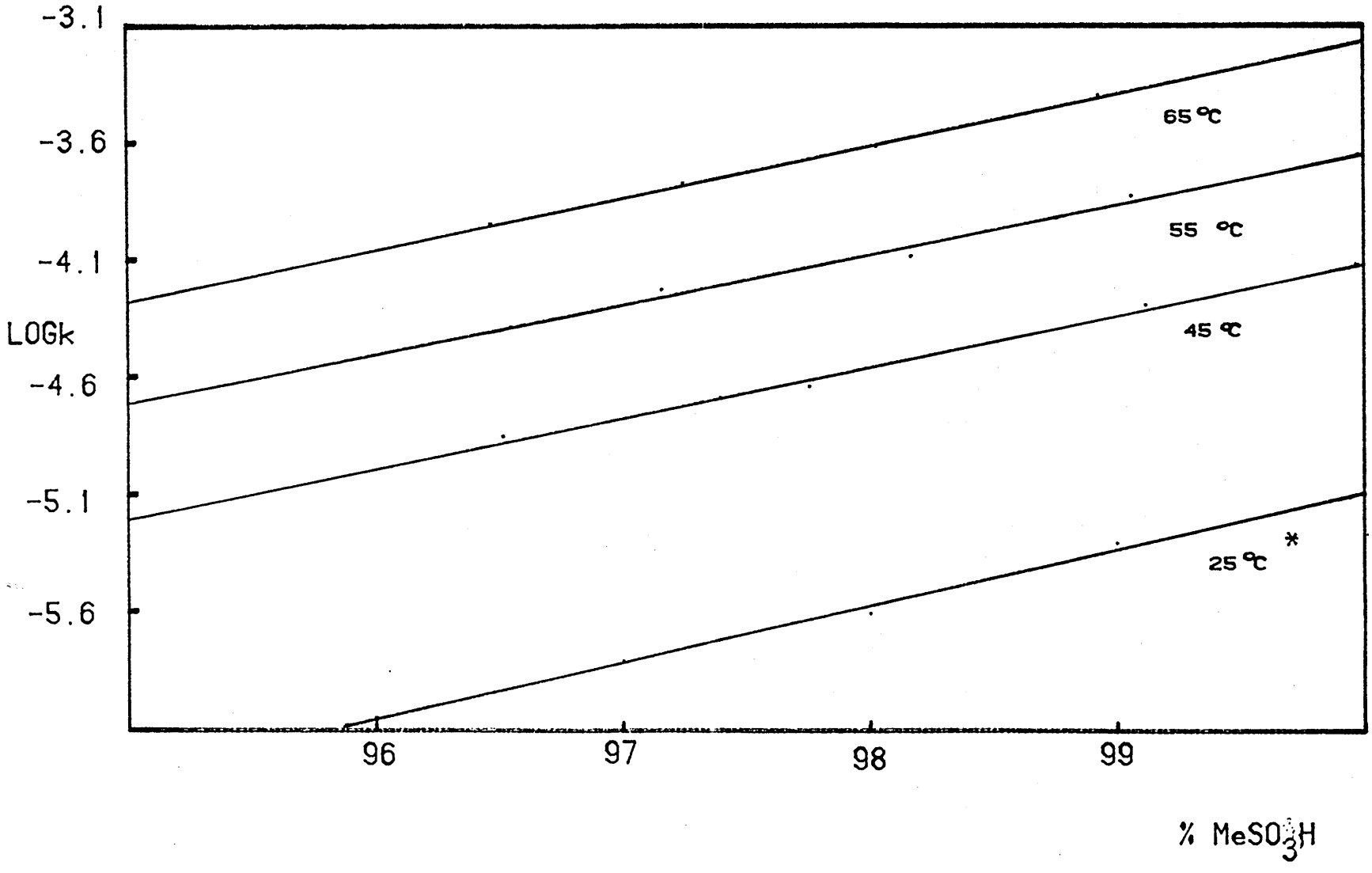
PLOT OF LOG k VS % $MeSO_3H$ ACID FOR DICI CPD (XIV)



PLOT OF LOG k VS % $MeSO_3H$ FOR DIPh CPD (XV)



PLOT OF LOGk vs % $MeSO_3H$ FOR DICL CPD (XIV)



* DATA EXTRAPOLATED FROM ARRHENIUS PLOTS

Acidity function data for methanesulphonic acid is very limited. The only acidity function that has been defined for the acidity range of interest is H_o,[22,23] but even this cannot be regarded as wholly acceptable. Whilst the data of R.C. Paul et al.[23] is useful it does not mention the temperature at which the work was carried out. Despite this drawback we shall interpret our results using this acidity function since the work of Katritzky et al.[24,25] shows that the effect of temperature on the acidity function would not be large over the temperature range expected. The data of Bascombe and Bell[22] will be used in conjunction with that of Paul et al.[23] This is because Bascombe's data is only really useful for acidities up to 90%. Paul's data which is for the range 90-100% can therefore be used to increase the range to 100% methanesulphonic acid. Other acidity functions for methanesulphonic acid are less well defined. H_R type data is not available for any range of acidity and work was performed in this project to cover the range 85-100%. The acidity function H_{GF} has also been defined,[26] in this medium. This scale was obtained using redox systems by measuring the electrode potential between a ferrocene/ferricinium ion and a hydrogen glass electrode. In such a study the need for an overlapping series of indicators is unnecessary. Unfortunately, however, the acidity range covered for this function is only 1-87.6% and hence it cannot be used in this work.

Using a combination of Bascombe's and Paul's[22,23] data for H_o, plots were obtained of log k against H_o for all benzylbenzoic acids studied. As mentioned earlier (section 6 of the Introduction) the slopes of such plots are helpful in elucidating the nature of the transition state, a slope of about 1 being indicative of a transition state resembling the protonated substrate. A number of these plots have been reproduced in the following pages together with the kinetic and acidity function data

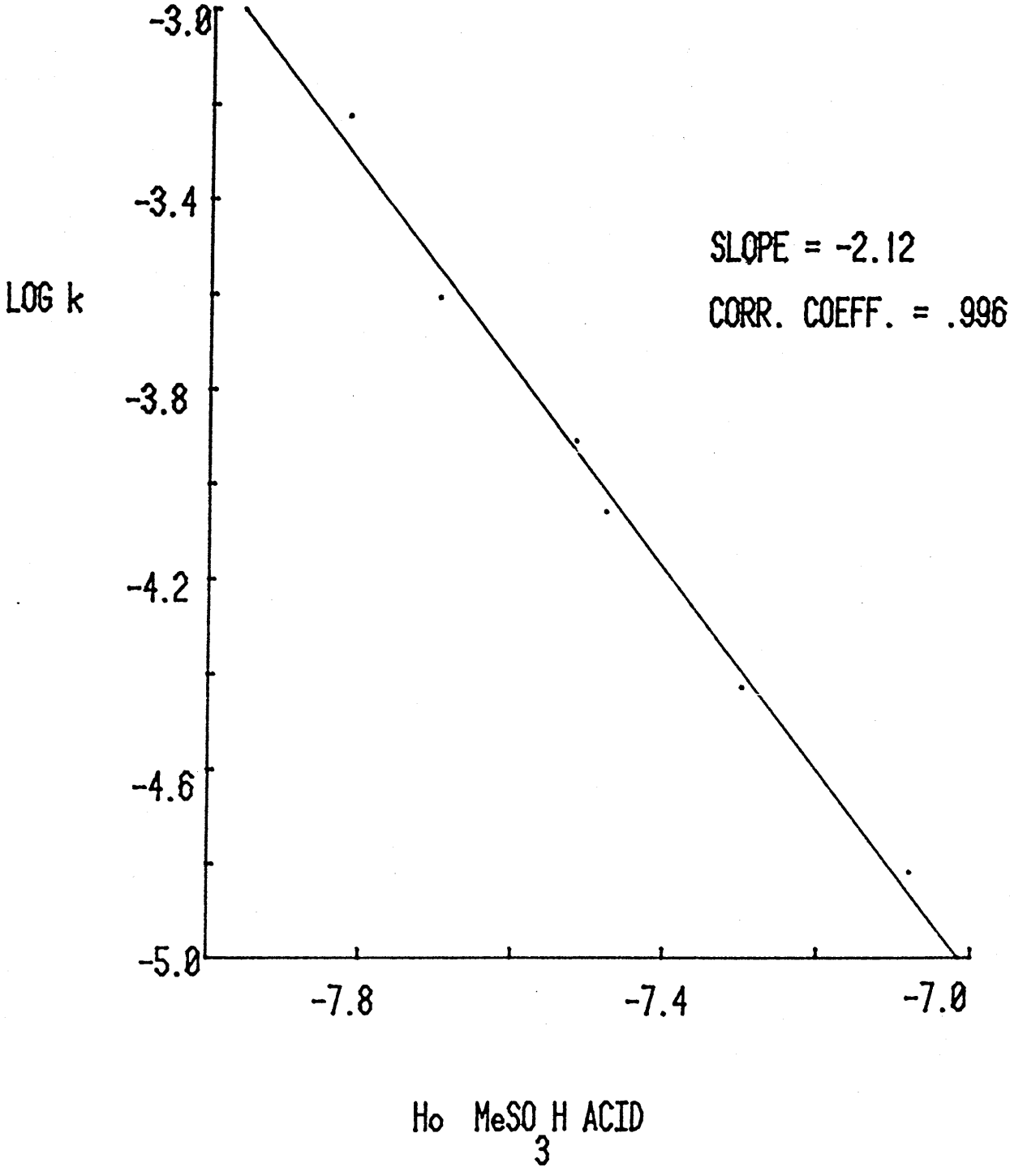
for each compound. The results are similar to those obtained for the plots against % acid. A linear correlation is observed for all cases, but in this case the slopes are unity or greater (Table 3.42). The slopes of compounds with a deactivating group (i.e. Cl or F) in the benzyl ring are extremely high. For example 2(3-fluorobenzyl)benzoic acid has a slope of 2.83 whereas 2(3-tolyl)benzoic acid has a slope of only 1.61. For a number of compounds the slopes lie in the range 1-1.7 and, as discussed later, this is in accord with a transition state for the rate limiting step that resembles the protonated benzylbenzoic acid. Where gradients of 2 or more are observed interpretation becomes less straight forward. In the past slopes of 2 and 3 have been thought to be a consequence of diprotonated or triprotonated transition states,[27] however, this clearly cannot be the case for benzylbenzoic acids since there is only one basic centre.

Table 3.42 Data on plots of log k vs H_o (methanesulphonic acid) for benzylbenzoic acids

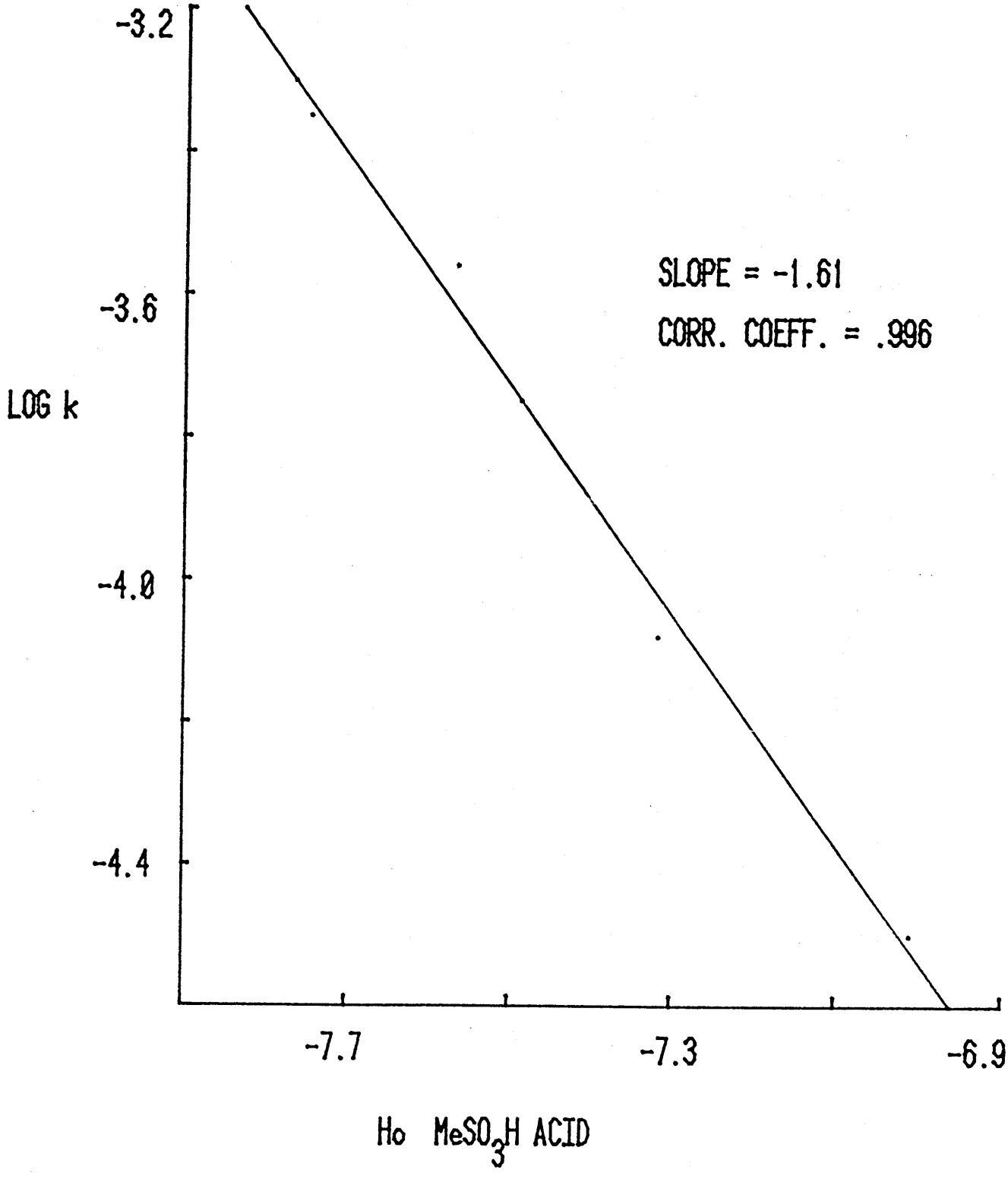
Compound	Slope/ Ho[a]	Corr. Coeff.	Slope/ Ho[b]	Corr. Coeff.	No. of points
2(3-Hydroxybenzyl)benzoic acid	-1.56	0.999	-1.30	0.999	5
2(3-Methoxybenzyl)benzoic acid	-1.89	0.990	-1.56	0.991	6
2(3-Tolyl)benzoic acid	-1.61	0.996	-1.32	0.997	6
2(4-Tolyl)benzoic acid	-1.70	0.993	-1.43	0.996	5
2(4-Methoxybenzyl)benzoic acid	-1.45	0.990	-1.13	0.980	5
2(4-Hydroxybenzyl)benzoic acid	-1.65	0.993	-1.37	0.992	5
2-Benzylbenzoic acid	-2.12	0.996	-1.75	0.997	6
2(3-Fluorobenzyl)benzoic acid	-2.83	0.997	-1.85	0.984	5
2(3-Chlorobenzyl)benzoic acid	-3.03	0.994	-2.60	0.996	4
2(4-Fluorobenzyl)benzoic acid	-3.17	0.995	-2.55	0.998	4
2(4-Chlorobenzyl)benzoic acid	-4.17	0.990	-3.68	0.999	4
2(3-Tolyl)-4,5-dimethoxy-benzoic acid	-1.20	0.995	-1.11	0.998	11
2(3-Tolyl)-4,5-dimethyl-benzoic acid	-1.15	0.995	-1.04	0.995	10
2(3-Tolyl)-4,5-diphenyl-benzoic acid	-1.47	0.997	-1.23	0.998	6
2(3-Tolyl)-4,5-dichloro-benzoic acid	-1.53	0.995	-1.36	0.995	4

a - H_o data is a combination of both Bascombe[22] and Paul[23]
b - H_o data is that of Bascombe and Bell only[22]

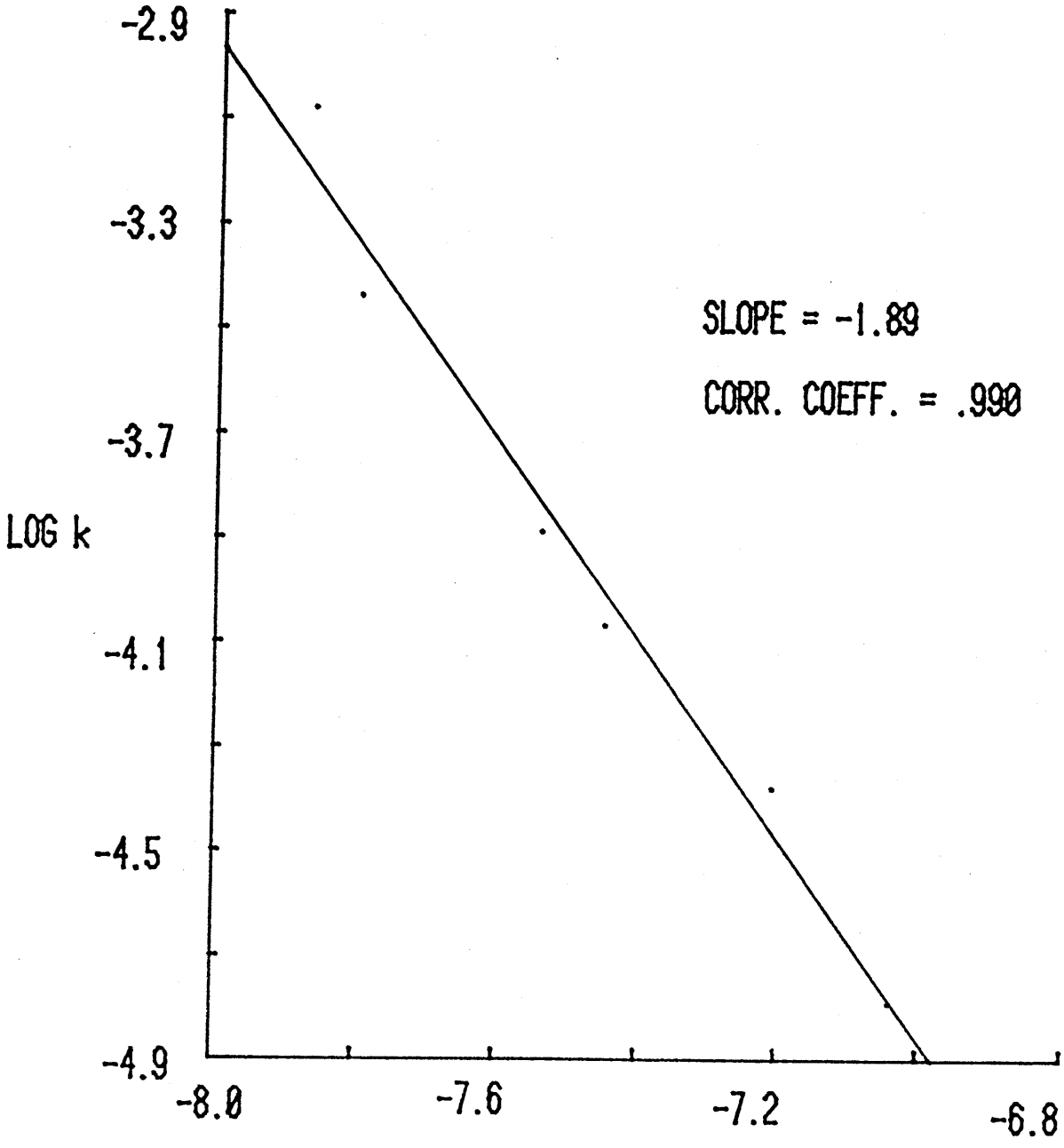
PLOT OF LOG k VS Ho FOR 2-D CPD (1a)



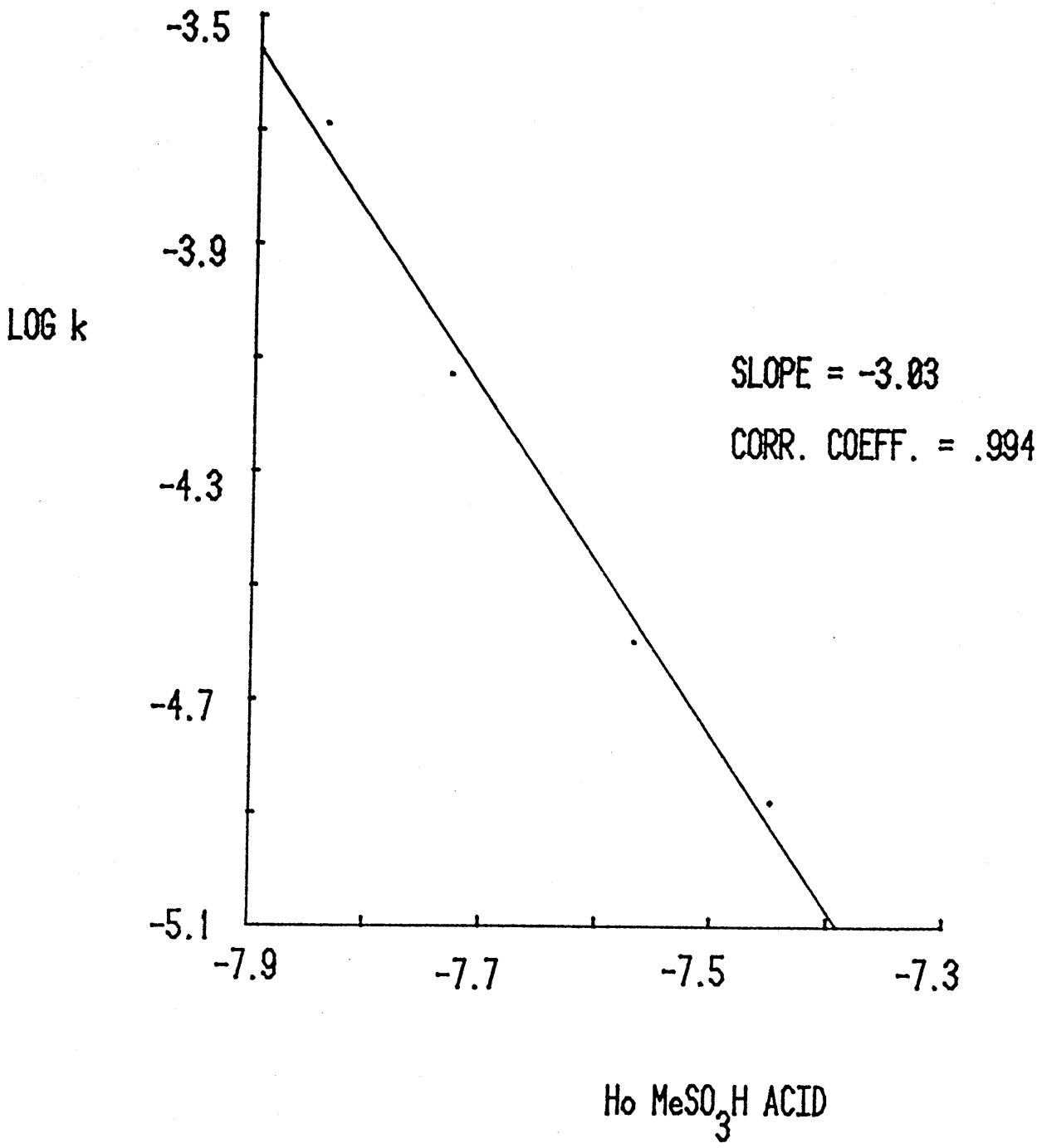
PLOT OF LOG k VS Ho FOR 3-ME CPD (II)



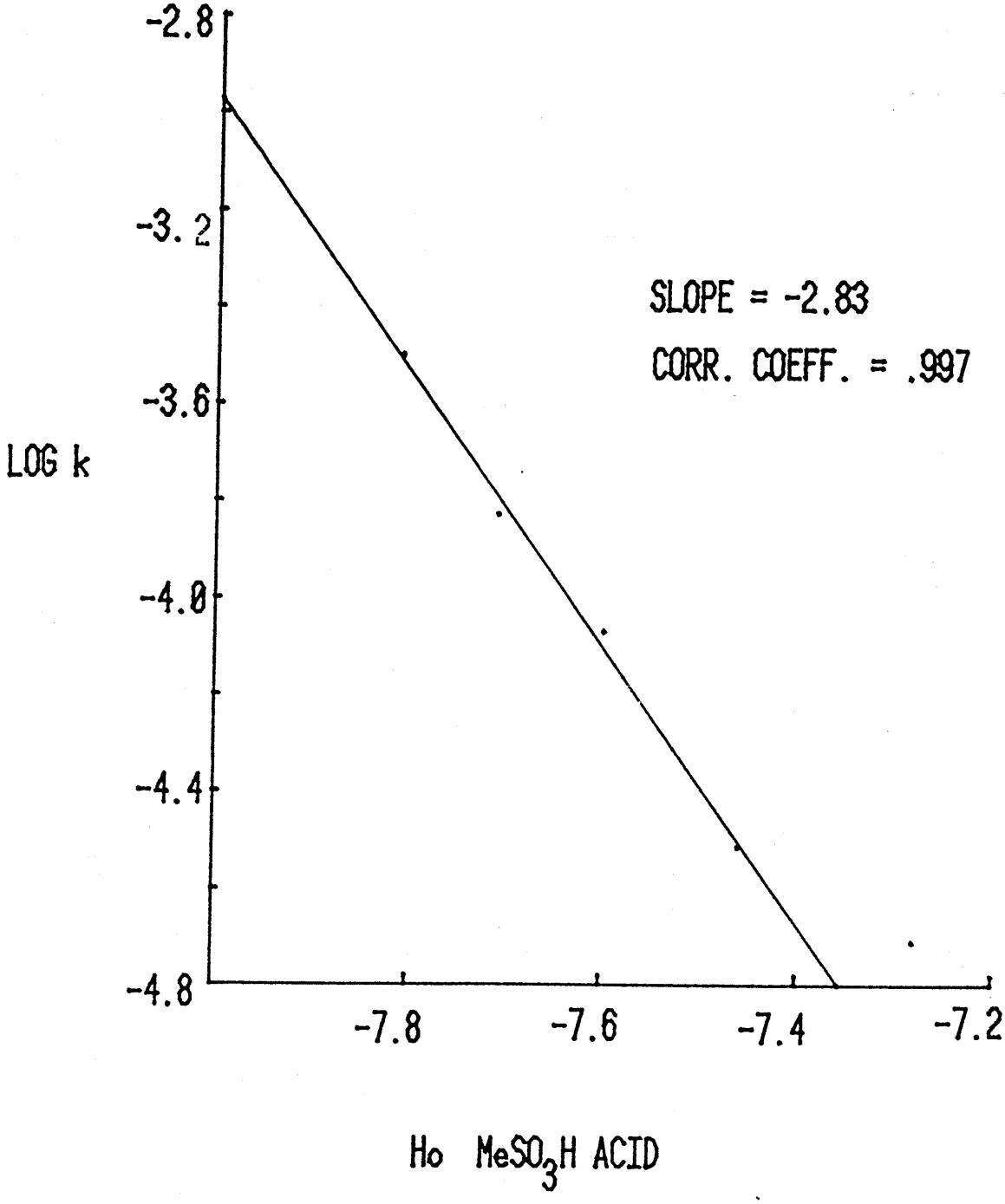
PLOT OF LOG k VS Ho FOR 3-MeO CPD (III)



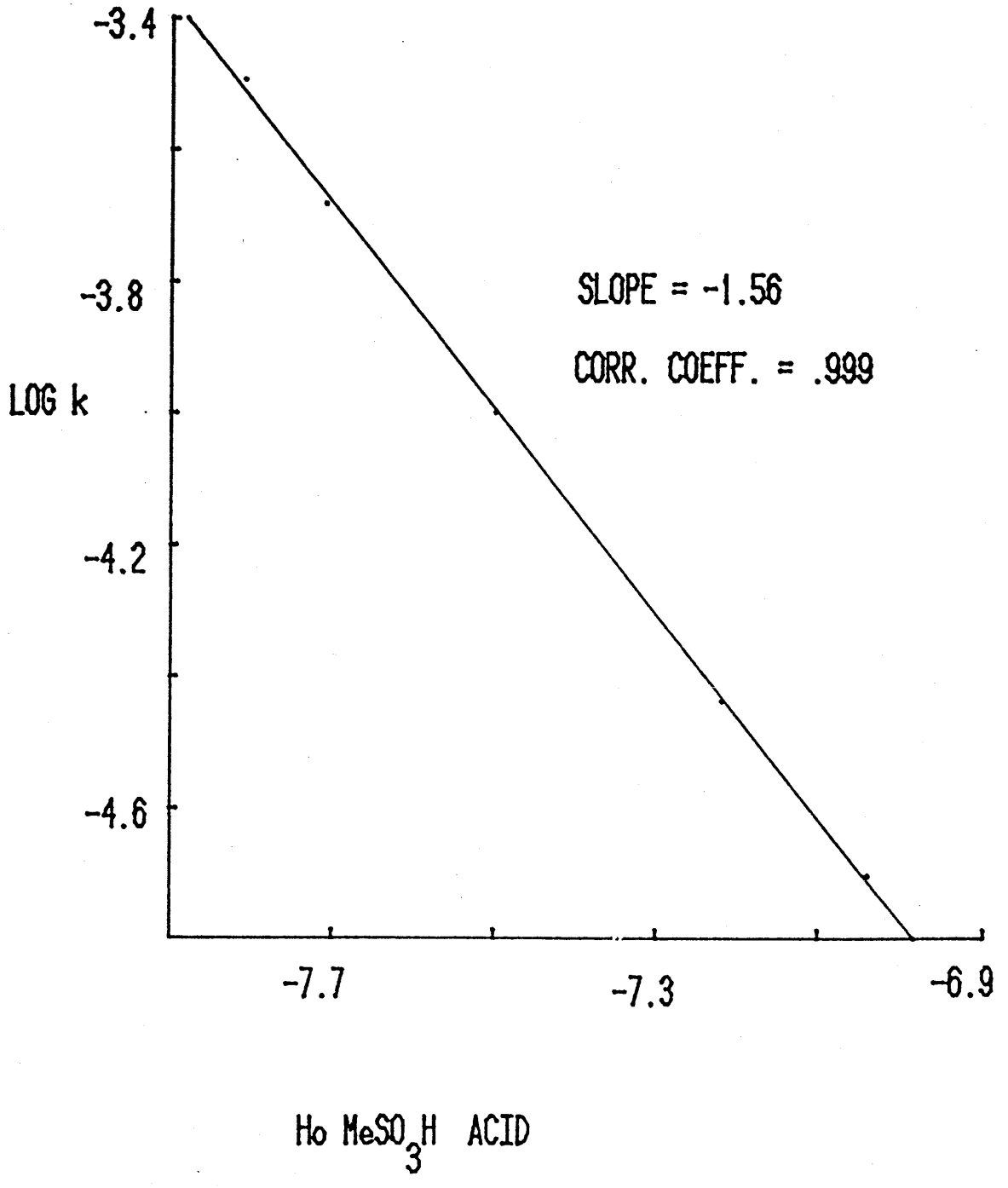
PLOT OF LOG k VS Ho FOR 3-Cl CPD (IV)



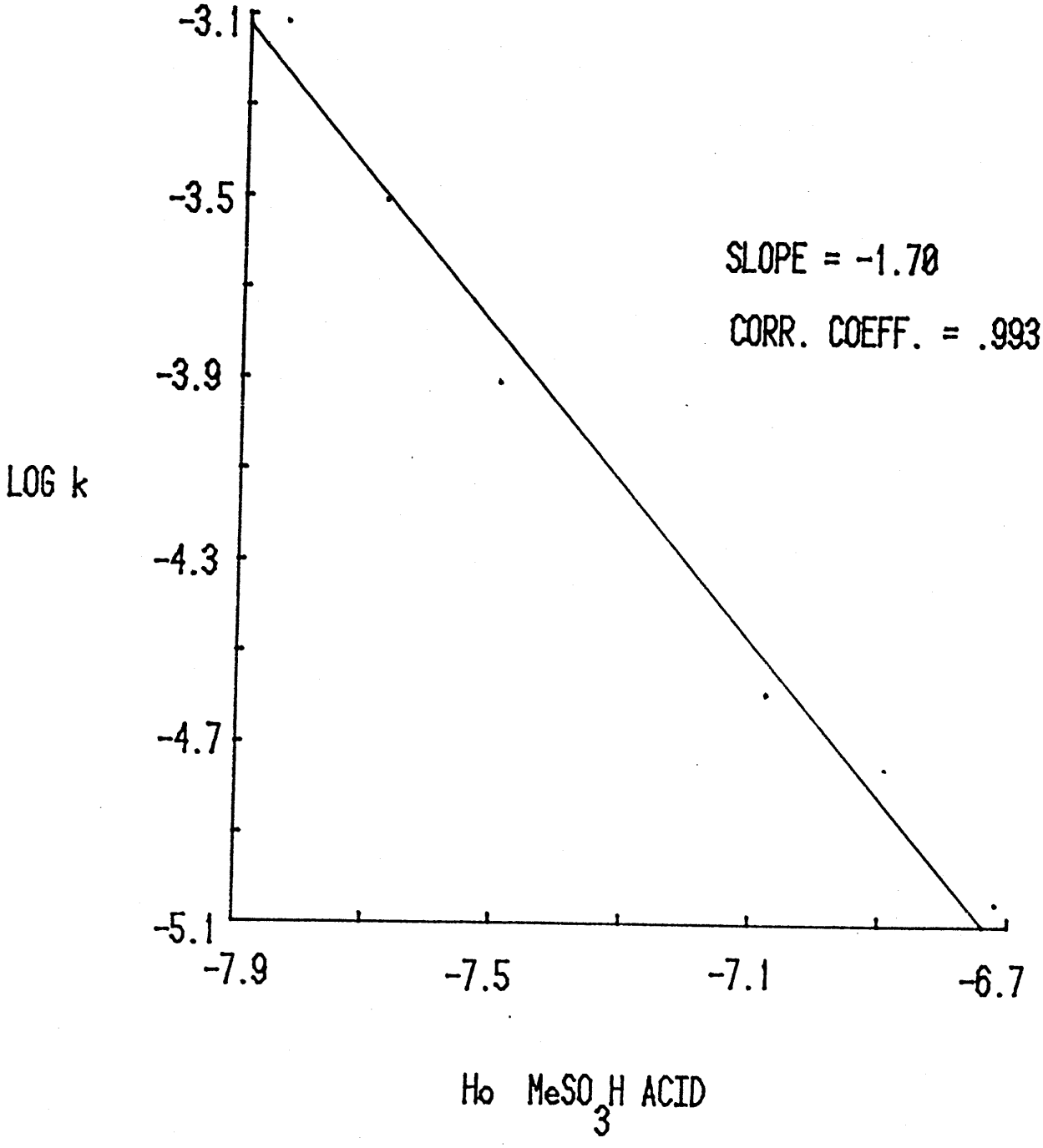
PLOT OF LOG k VS Ho FOR 3-F CPD (V)



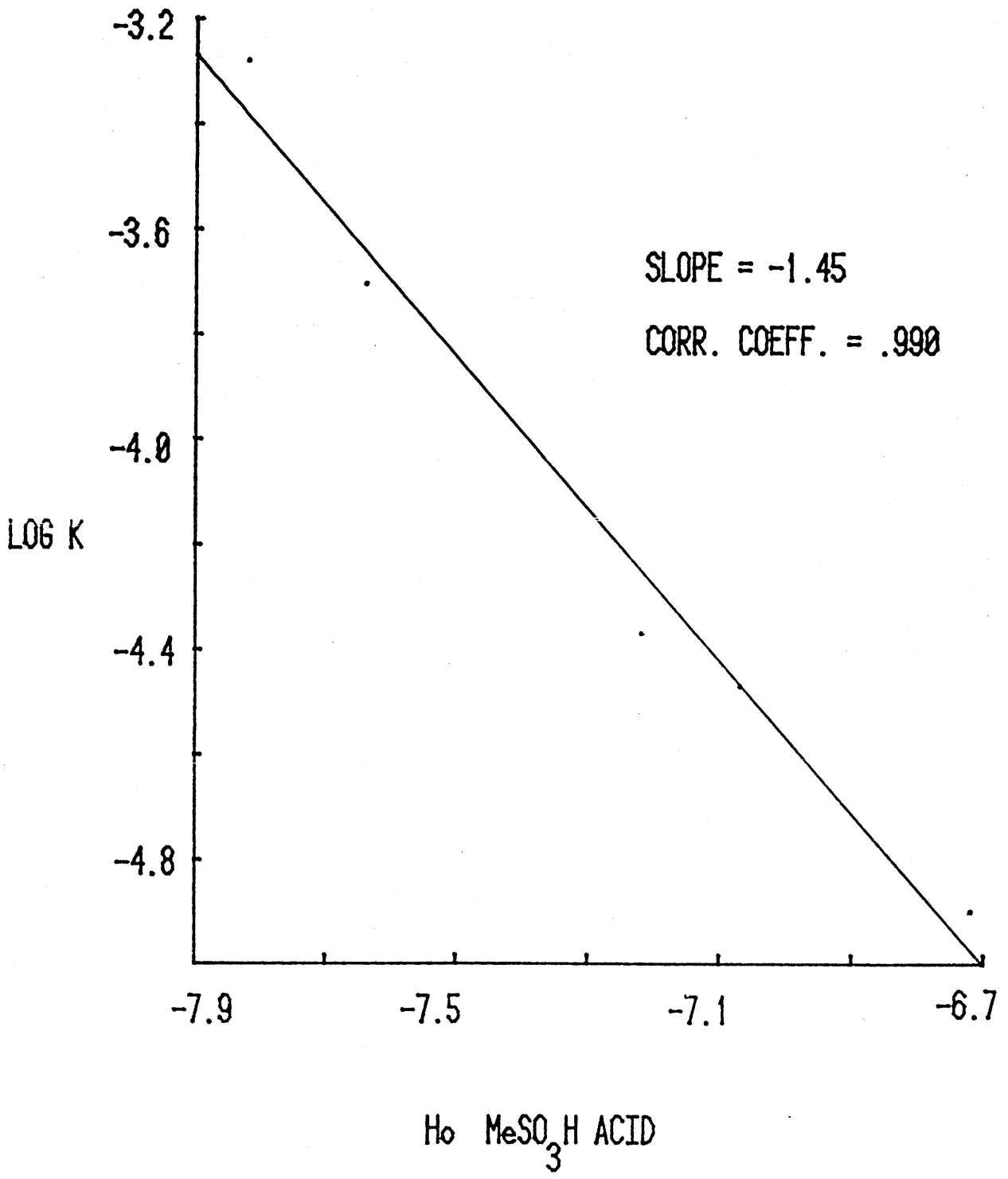
PLOT OF LOG k VS Ho FOR 3-OH CPD (VI)



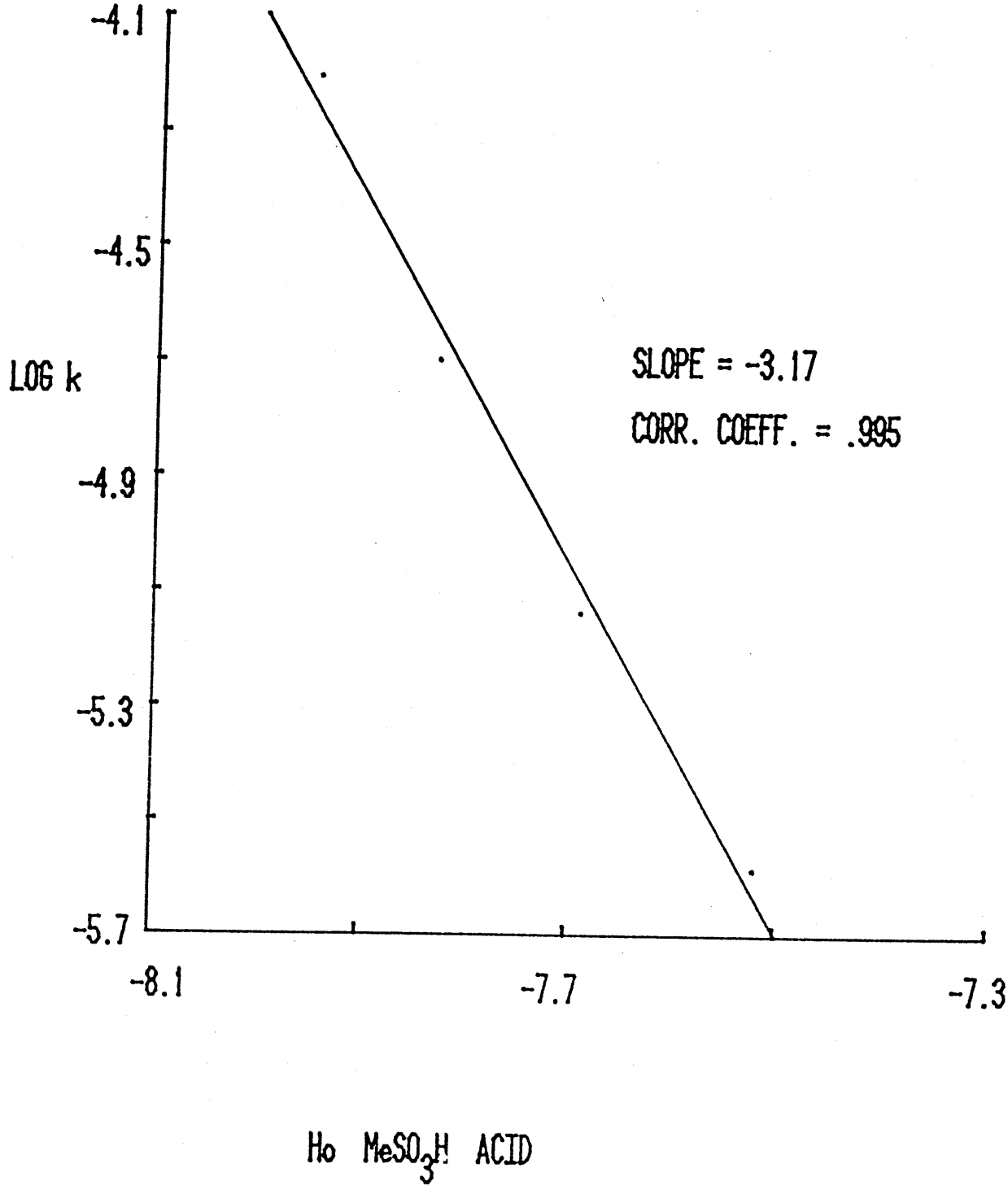
PLOT OF LOG k VS Ho FOR 4-Me CPD (VII)



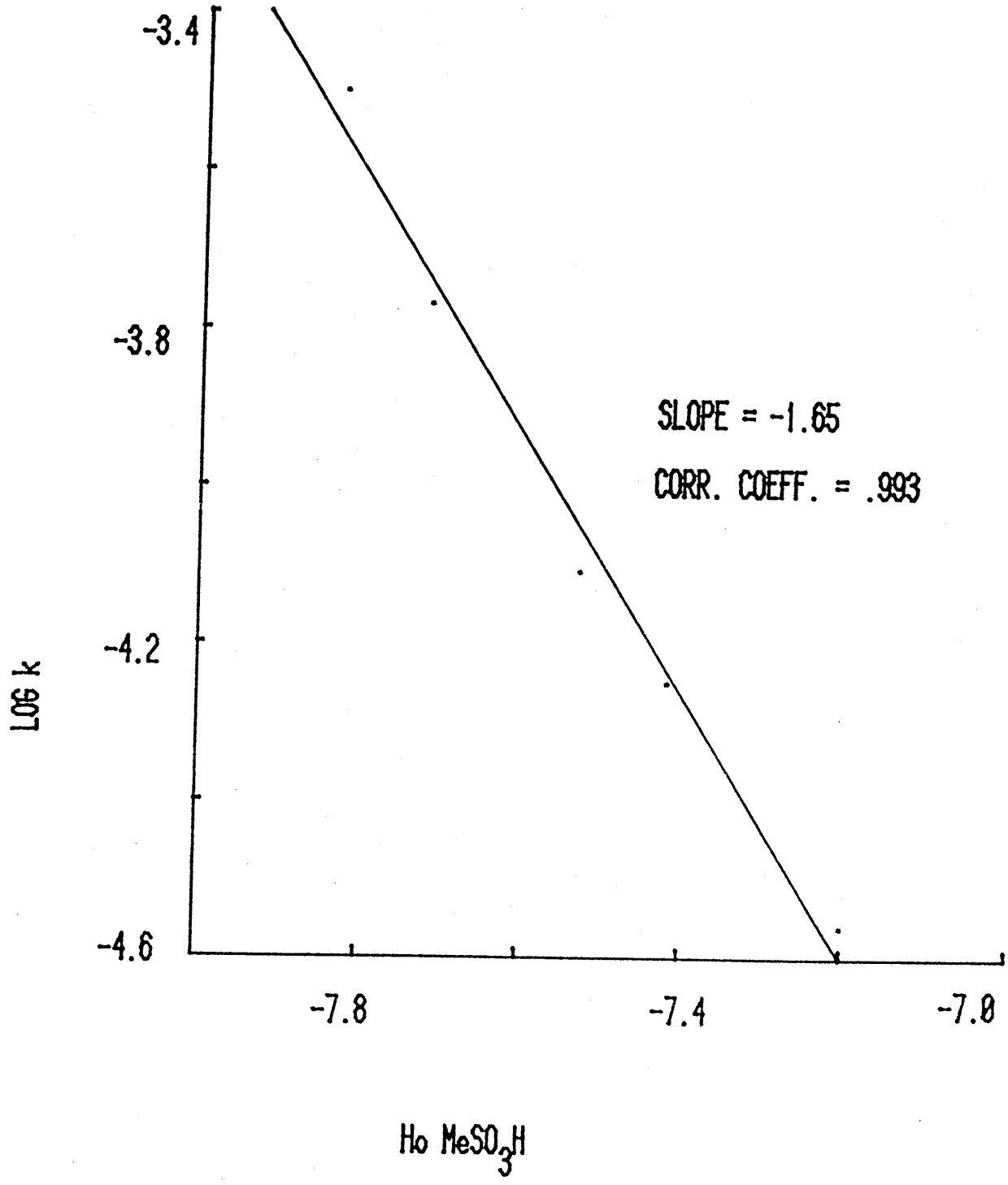
PLOT OF LOG k VS Ho FOR 4-MeO CPD (VIII)



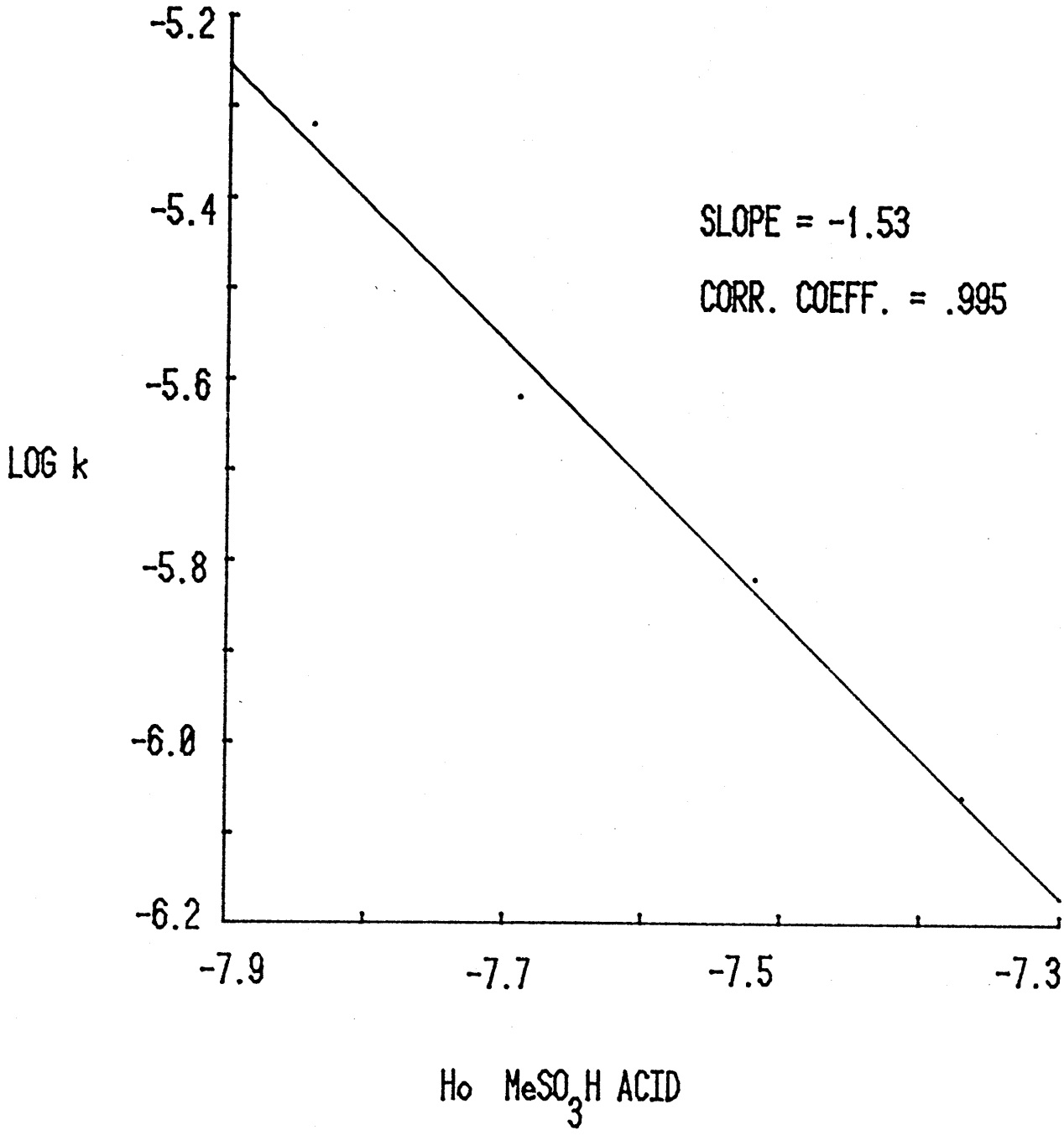
PLOT OF LOG k VS Ho FOR 4-F CPD (X)



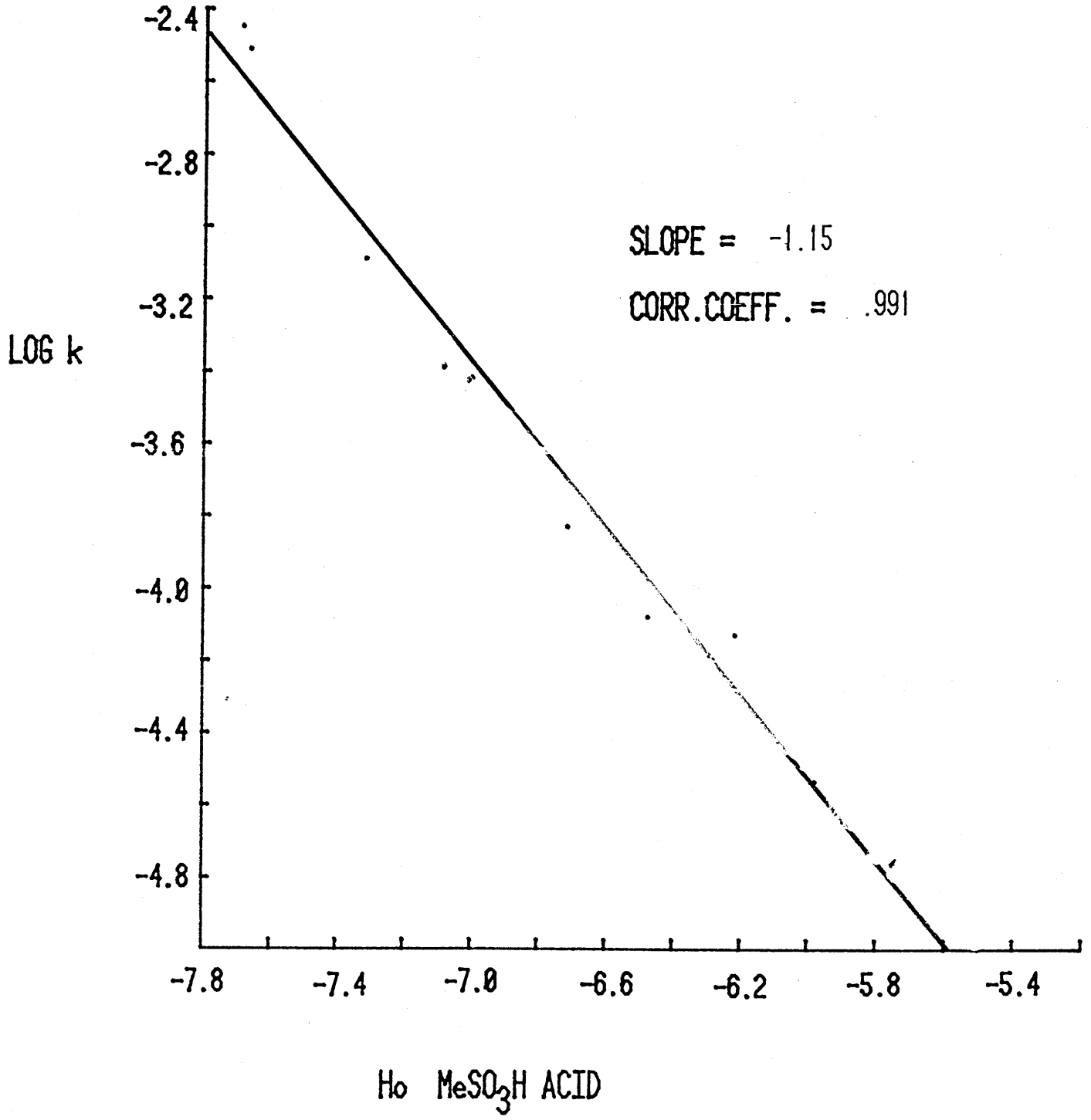
PLOT OF LOG k VS Ho FOR 4-OH CPD (XI)



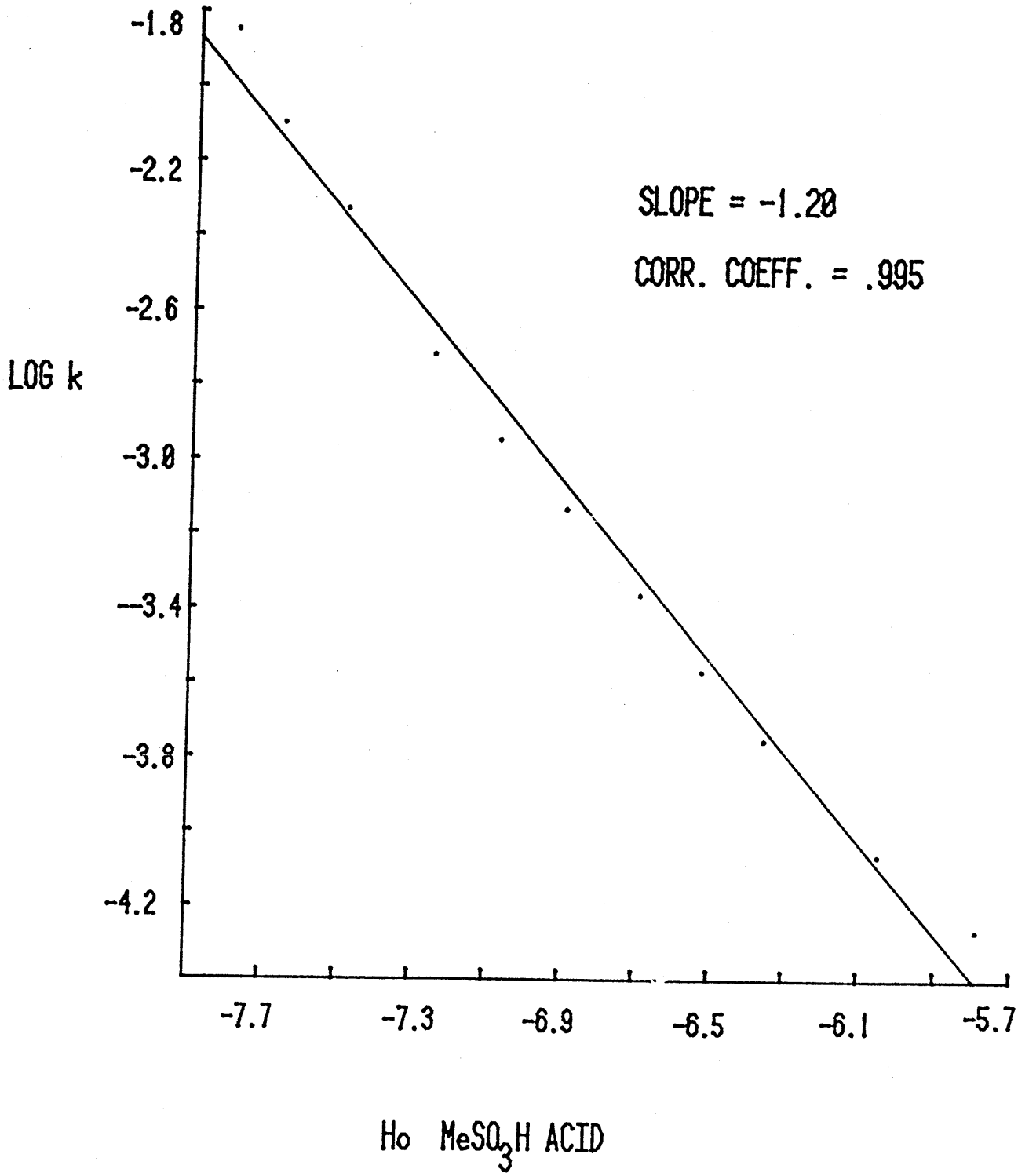
PLOT OF LOG k VS Ho FOR DICl CPD (XIV)



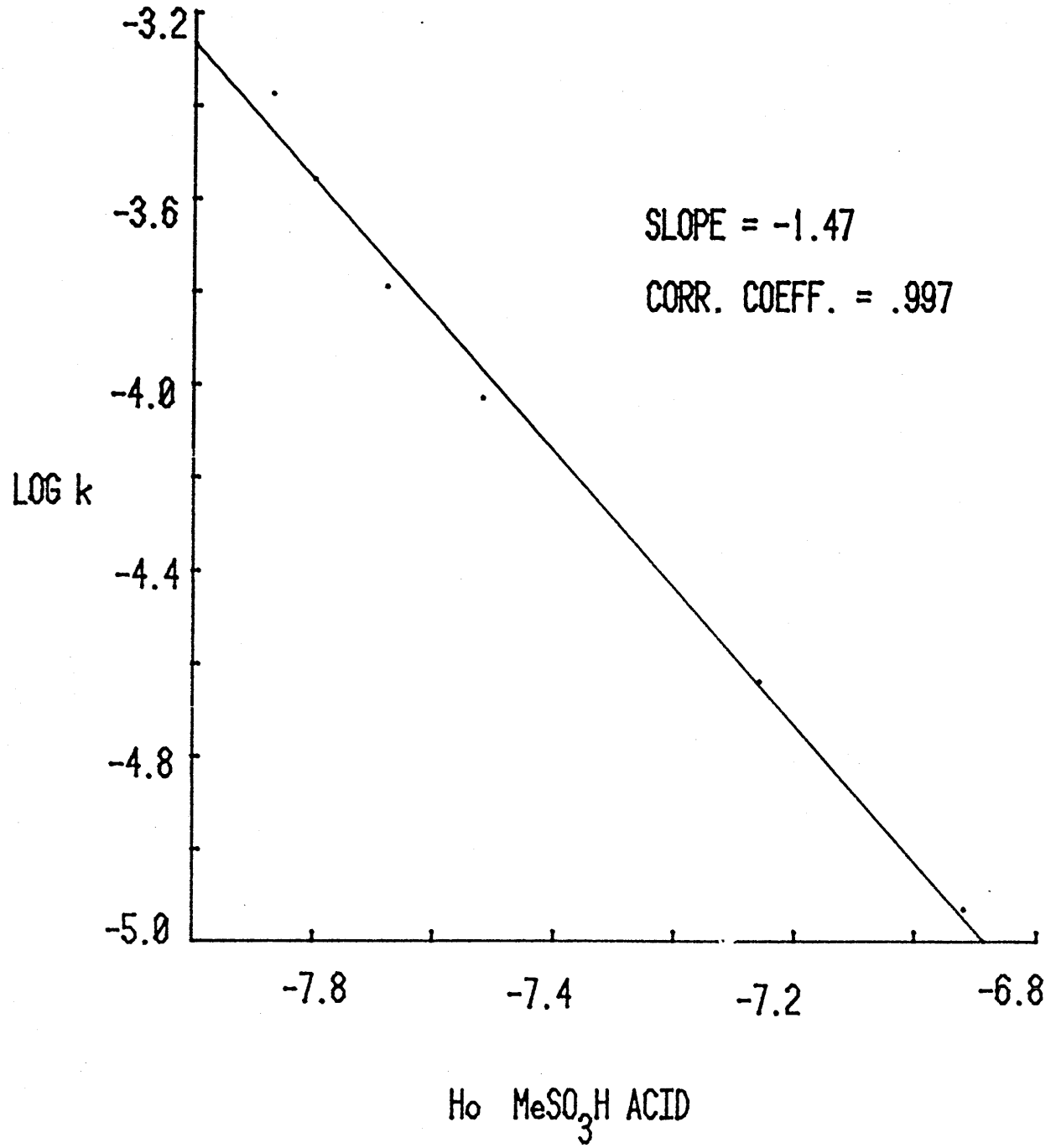
PLOT OF LOG k VS Ho FOR DIMe CPD (XII)



PLOT OF LOG k VS Ho FOR DIMeO CPD (XIII)



PLOT OF LOG k VS Ho FOR DIPh CPD (XV)



Kinetic data on the cyclisation of 2-benzylbenzoic acid in methanesulphonic acid at 25°C

% Acid	k/s^{-1}	log k	H_o
100	5.02×10^{-3}	-2.30	-
98.92	6.16×10^{-4}	-3.21	-7.82
98.06	2.51×10^{-4}	-3.60	-7.70
97.16	1.28×10^{-4}	-3.89	-7.52
96.64	8.98×10^{-5}	-4.05	-7.48
95.50	3.98×10^{-5}	-4.40	-7.30
94.13	1.47×10^{-5}	-4.83	-7.08

Kinetic data on the cyclisation of 2(2-deuterobenzyl)benzoic acid in methanesulphonic acid at 25°C

% Acid	k/s^{-1}	log k	H_o
100	4.99×10^{-3}	-2.302	-
98.06	2.43×10^{-4}	-3.614	-7.70
97.16	1.225×10^{-4}	-3.914	-7.52
96.64	8.715×10^{-5}	-4.06	-7.48
95.5	3.76×10^{-5}	-4.425	-7.3
94.13	1.50×10^{-5}	-4.824	-7.08
98.92	5.96×10^{-4}	-3.225	-7.82

Kinetic data on the cyclisation of 2(3-tolyl)benzoic acid in methanesulphonic acid at various temperatures

% Acid	Temp. °C	k/s^{-1}	log k	H_o
100	45	2.11×10^{-2}	-1.68	-
97.78	45	3.39×10^{-3}	-2.47	-
96.72	45	2.34×10^{-3}	-2.63	-
95.23	45	1.27×10^{-3}	-2.90	-
93.77	45	6.97×10^{-3}	-3.16	-
92.63	45	3.16×10^{-4}	-3.50	-
100	35	5.57×10^{-3}	-2.25	-
98.32	35	1.74×10^{-3}	-2.76	-
96.83	35	7.11×10^{-4}	-3.15	-
95.50	35	3.72×10^{-4}	-3.43	-
94.13	35	1.50×10^{-4}	-3.82	-
93.79	35	1.68×10^{-4}	-3.77	-
100	25	2.85×10^{-3}	-2.54	-
98.52	25	5.01×10^{-4}	-3.30	-7.77
98.42	25	4.47×10^{-4}	-3.35	-7.75
97.28	25	2.77×10^{-4}	-3.56	-7.57
96.81	25	1.77×10^{-4}	-3.75	-7.49
95.71	25	8.32×10^{-5}	-4.08	-7.32
93.69	25	3.16×10^{-5}	-4.50	-7.01

Kinetic data on the cyclisation of 2(3-methoxybenzyl)benzoic acid in methanesulphonic acid at 25°C

% Acid	k/s^{-1}	log k	H_o
100	1.72×10^{-3}	-2.76	-
99.28	8.39×10^{-4}	-3.08	-7.87
98.77	3.64×10^{-4}	-3.44	-7.80
97.04	1.28×10^{-4}	-3.89	-7.54
96.5	8.44×10^{-5}	-4.07	-7.45
94.95	4.15×10^{-5}	-4.38	-7.21
93.92	1.63×10^{-5}	-4.79	-7.04

Kinetic data on the cyclisation of 2(3-chlorobenzyl)benzoic acid in methanesulphonic acid at 25°C

% Acid	k/s^{-1}	log k	H_o
100	5.71×10^{-4}	-3.24	-
99.01	2.06×10^{-4}	-3.69	-7.84
98.3	7.45×10^{-5}	-4.13	-7.73
97.33	2.51×10^{-5}	-4.60	-7.57
96.55	1.32×10^{-5}	-4.88	-7.45

Kinetic data on the cyclisation of 2(3-fluorobenzyl)benzoic acid in methanesulphonic acid at 25°C

% Acid	k/s^{-1}	log k	H_o
100	6.11×10^{-3}	-2.21	-
98.8	3.14×10^{-4}	-3.50	-7.81
98.14	1.48×10^{-4}	-3.83	-7.71
97.49	8.45×10^{-5}	-4.07	-7.60
96.52	3.05×10^{-5}	-4.51	-7.46
95.28	1.95×10^{-5}	-4.71	-7.28

Kinetic data on the cyclisation of 2(3-hydroxybenzyl)benzoic acid in methanesulphonic acid

% Acid	k/s^{-1}	log k	H_o
98.78	3.195×10^{-4}	-3.49	-7.81
98.14	2.073×10^{-4}	-3.68	-7.71
96.89	9.94×10^{-5}	-4.00	-7.5
95.02	3.65×10^{-5}	-4.44	-7.22
93.91	1.98×10^{-5}	-4.70	-7.04

Kinetic data on the cyclisation of 2(4-tolyl)benzoic acid in methanesulphonic acid at 25°C

% Acid	k/s^{-1}	log k	H_o
100	6.73×10^{-3}	-2.17	-
99.04	7.57×10^{-4}	-3.12	-7.84
97.97	3.10×10^{-4}	-3.51	-7.68
96.73	1.23×10^{-4}	-3.91	-7.50
94.11	2.57×10^{-5}	-4.59	-7.08
92.04	8.93×10^{-6}	-5.05	-6.72

Kinetic data on the cyclisation of 2(4-methoxybenzyl)benzoic acid in methanesulphonic acid at 25°C

% Acid	k/s^{-1}	log k	H_o
100	5.739×10^{-3}	-2.23	-
98.88	5.301×10^{-4}	-3.28	-7.82
97.72	1.974×10^{-4}	-3.71	-7.64
95.01	4.257×10^{-5}	-4.37	-7.22
94.06	3.413×10^{-5}	-4.47	-7.07
91.99	1.25×10^{-5}	-4.90	-6.72

Kinetic data on the cyclisation of 2(4-chlorobenzyl)benzoic acid in methanesulphonic acid at 25°C

% Acid	k/s^{-1}	log k	H_o
99.48	2.58×10^{-5}	-4.59	-7.9
99.01	1.18×10^{-5}	-4.93	-7.84
98.07	2.73×10^{-6}	-5.56	-7.70
96.97	4.12×10^{-7}	-6.38	-7.52

Kinetic data on the cyclisation of 2(4-fluorobenzyl)benzoic acid in methanesulphonic acid at 25°C

% Acid	k/s^{-1}	log k	H_o
99.94	6.19×10^{-5}	-4.21	-7.95
98.96	2.00×10^{-5}	-4.70	-7.83
98.04	7.17×10^{-6}	-5.14	-7.69
97.01	2.63×10^{-6}	-5.59	-7.52

Kinetic data on the cyclisation of 2(4-hydroxybenzyl)benzoic acid in methanesulphonic acid at 25°C

% Acid	k/s^{-1}	log k	H_o
98.84	3.15×10^{-4}	-3.50	-7.83
98.21	1.7×10^{-4}	-3.77	-7.72
97.04	7.78×10^{-5}	-4.11	-7.53
94.9	2.72×10^{-5}	-4.56	-7.2
96.32	5.59×10^{-5}	-4.25	-7.42

Kinetic data on the cyclisation of 2(3-tolyl)-4,5-dimethylbenzoic acid in methanesulphonic acid at 25°C

% Acid	k/s^{-1}	log k	H_o
99.00	7.42×10^{-3}	-2.13	-
98.04	3.53×10^{-3}	-2.45	-7.69
97.88	3.06×10^{-3}	-2.51	-7.67
95.61	8.20×10^{-4}	-3.09	-7.32
94.22	4.11×10^{-4}	-3.39	-7.09
93.77	3.80×10^{-4}	-3.42	-7.02
92.04	1.49×10^{-4}	-3.83	-6.72
90.66	8.74×10^{-5}	-4.08	-6.48
89.26	7.42×10^{-5}	-4.13	-6.22
88.01	2.94×10^{-5}	-4.53	-5.98
86.78	1.79×10^{-5}	-4.75	-5.75

Kinetic data on the cyclisation of 2(3-tolyl)-4,5-dimethoxybenzoic acid in methanesulphonic acid at 25°C

% Acid	k/s^{-1}	log k	H_o
98.78	1.41×10^{-2}	-1.85	-7.8
97.91	7.95×10^{-3}	-2.10	-7.67
96.86	4.72×10^{-3}	-2.33	-7.50
95.30	1.89×10^{-3}	-2.72	-7.26
94.15	1.11×10^{-3}	-2.95	-7.08
93.04	7.25×10^{-4}	-3.14	-6.9
91.93	4.31×10^{-4}	-3.37	-6.7
90.91	2.70×10^{-4}	-3.57	-6.53
90.02	1.76×10^{-4}	-3.76	-6.36
88.33	8.58×10^{-5}	-4.06	-6.05
86.96	5.39×10^{-5}	-4.27	-5.79

Kinetic data on the cyclisation of 2(3-tolyl)-4,5-dichlorobenzoic acid in methanesulphonic acid at various temperatures

% Acid	Temp. °C	k/s^{-1}	log k	H_o
98.93	65	3.95×10^{-4}	-3.40	-
98.03	65	2.37×10^{-4}	-3.63	-
97.25	65	1.65×10^{-4}	-3.78	-
96.47	65	1.10×10^{-4}	-3.96	-
99.06	55	1.49×10^{-4}	-3.83	-
98.17	55	8.27×10^{-5}	-4.08	-
97.16	55	5.93×10^{-5}	-4.23	-
96.55	55	4.10×10^{-5}	-4.39	-
99.12	45	5.17×10^{-5}	-4.29	-
97.76	45	2.32×10^{-5}	-4.64	-
97.40	45	2.08×10^{-5}	-4.68	-
96.52	45	1.42×10^{-5}	-4.85	-
99.00	25[a]	4.79×10^{-6}	-5.35	-7.84
98.00	25[a]	2.40×10^{-6}	-5.62	-7.69
97.00	25[a]	1.51×10^{-6}	-5.82	-7.52
96.00	25[a]	8.71×10^{-7}	-6.06	-7.37

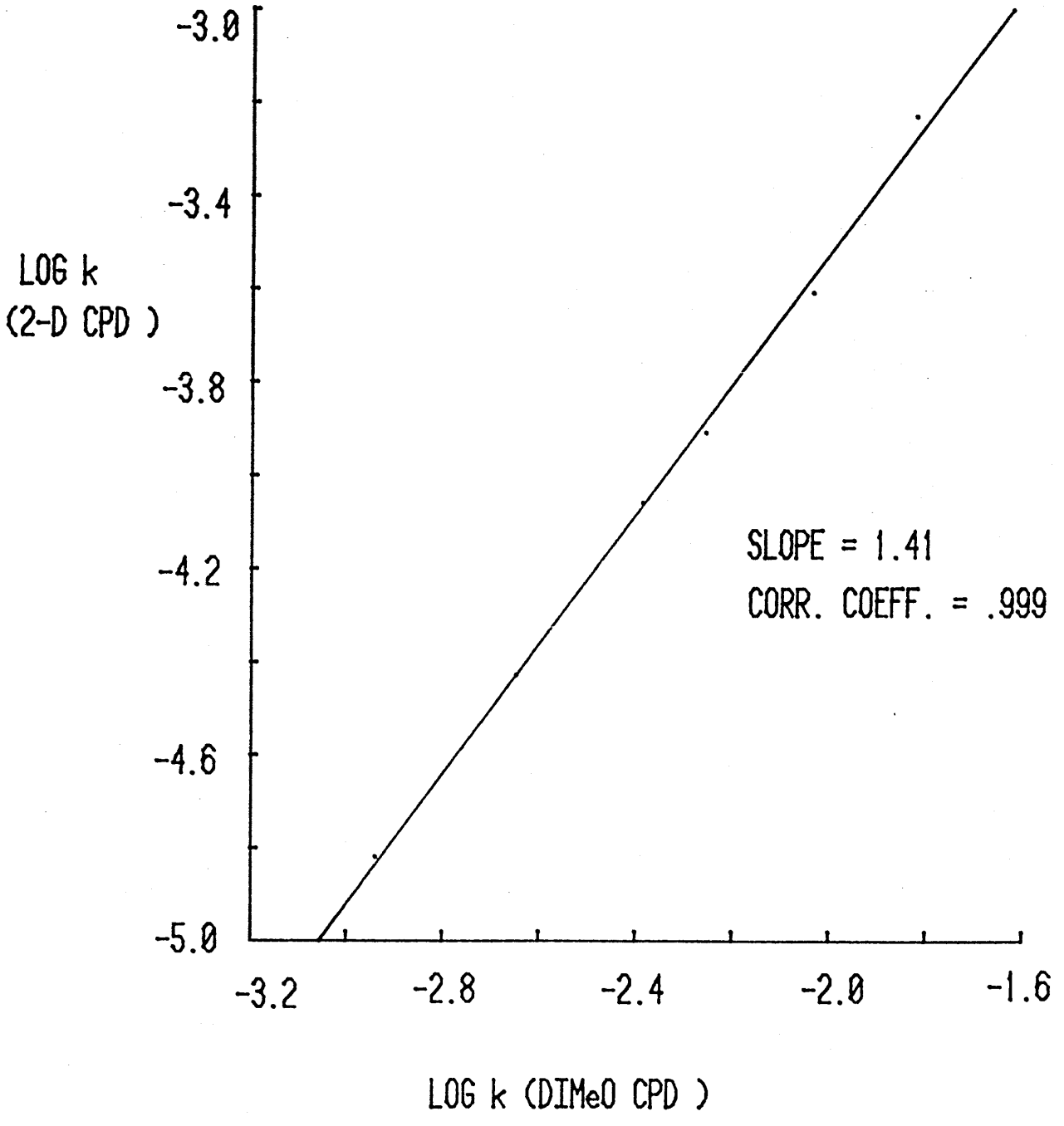
a - Data extrapolated from Arrhenius plots.

Kinetic data on the cyclisation of 2(3-tolyl)-4,5-diphenylbenzoic acid in methanesulphonic acid at 25°C

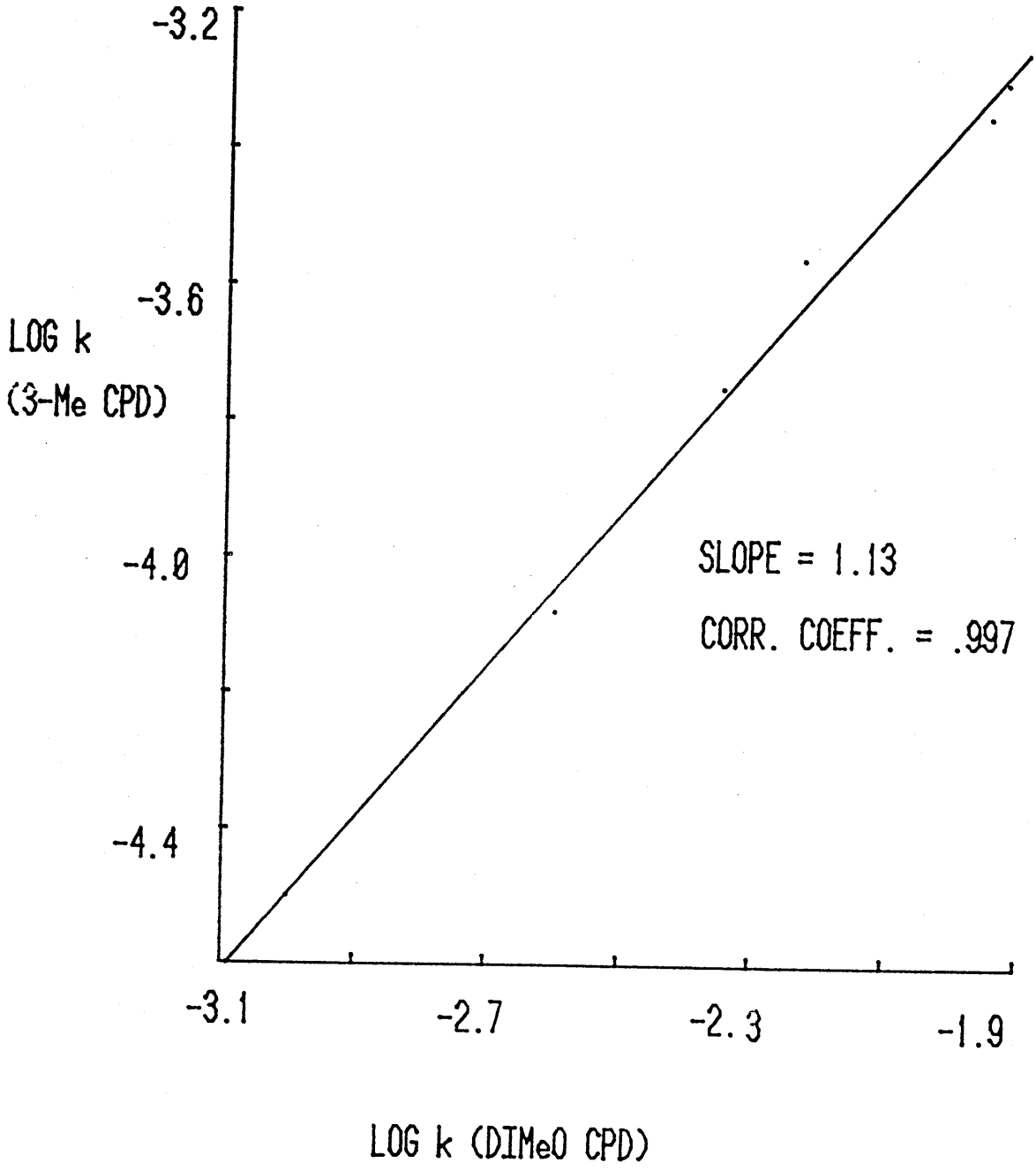
% Acid	k/s^{-1}	log k	H_o
99.28	4.22×10^{-4}	-3.38	-7.87
98.74	2.77×10^{-4}	-3.56	-7.8
97.96	1.63×10^{-4}	-3.79	-7.68
96.97	9.36×10^{-5}	-4.03	-7.52
94.02	2.30×10^{-5}	-4.64	-7.06
92.06	7.42×10^{-6}	-5.13	-6.72

The dramatic increase in the slope of log k vs H_o occurs for compounds containing deactivating groups. These compounds thus require stronger acid for cyclisation and the acidity range studied is thus higher than those compounds containing activating groups. So the change in slope could be a result of an H_o scale that is poorly defined at higher acidity and in this region the graph of H_o VS % acid should be much steeper as is found for sulphuric acid.[28,29] This can be ruled out following from two pieces of evidence. Firstly 2(3-tolyl)-4,5-dimethyl benzoic acid has been studied across the range (86.96 - 98.78%). This is a reasonable straight line across the entire range with a slope of -1.15 against H_o (see p.164). There is a small upward curvature in the region of 96 - 100% acid which is also detectable in plots of log k vs H_o for one or two other compounds, but this is too small to account for the dramatic increase in slopes for compounds containing deactivating groups. Since 2(3-tolyl)-4,5-dimethoxybenzoic acid has been measured across the entire range employed for all compounds it can be used as a kinetic acidity function[30] since the rates will mirror the changes in acidity. Table 3.41 shows the gradients obtained from plots of log k for the various benzylbenzoic acids versus log k for 2(3-tolyl)-4,5-dimethoxybenzoic acid; some of these plots are reproduced in the following pages. These latter rate constants were obtained by interpolation from the raw data. Again the changes in the slope are clearly manifested. The second piece of evidence which supports the present H_o data comes from studies on the corresponding series of 2-benzylbenzaldehydes which has been examined in a similar range of acidities (Table 3.43), in this case compounds containing electron withdrawing groups are well behaved, most compounds having slopes between 0.13 and 0.18 against % acid and 0.85 and 1.15 against H_o.

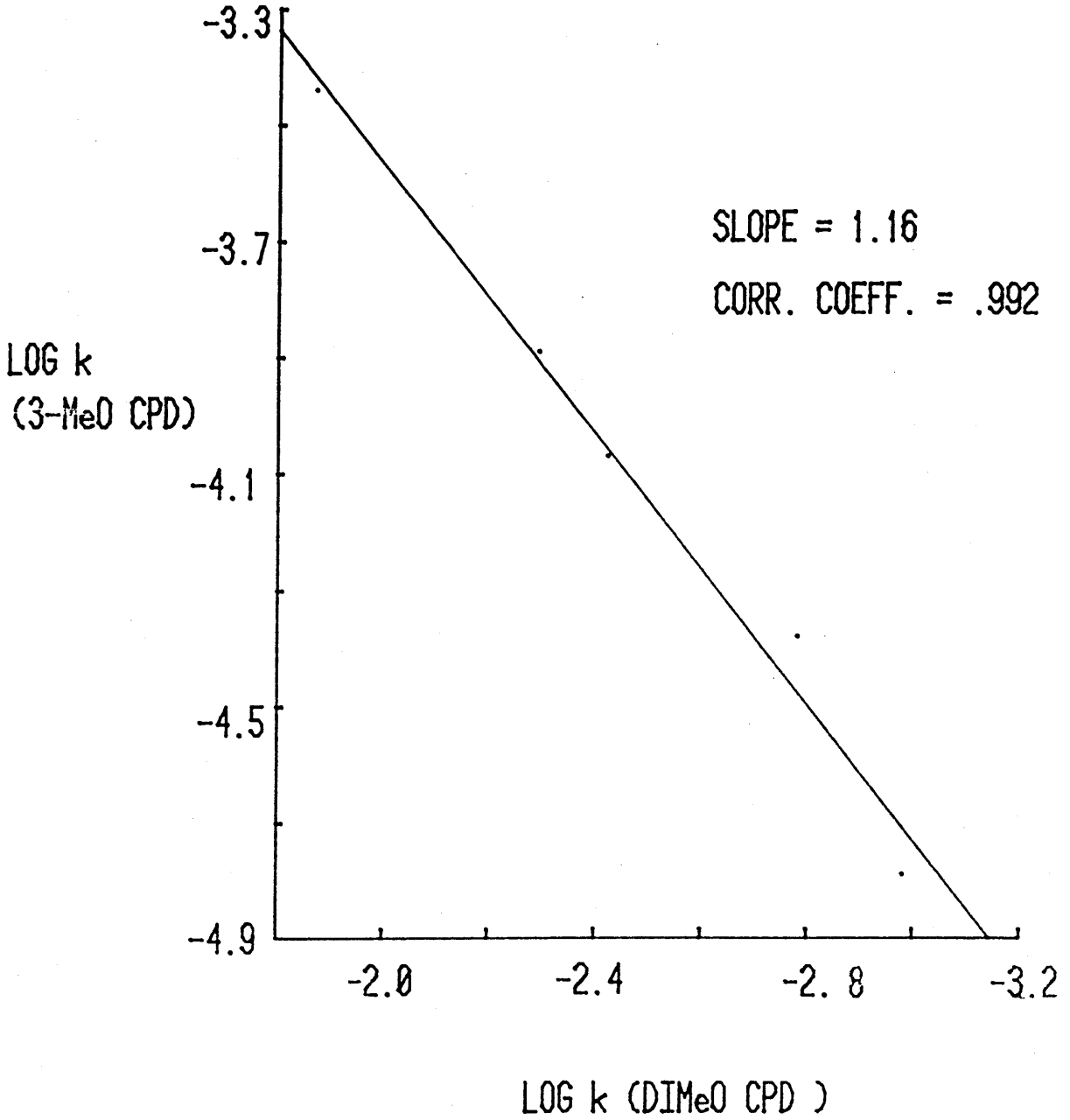
PLOT OF LOG k (2-D CPD Ia) VS LOG k (DIMeO CPD XIII)



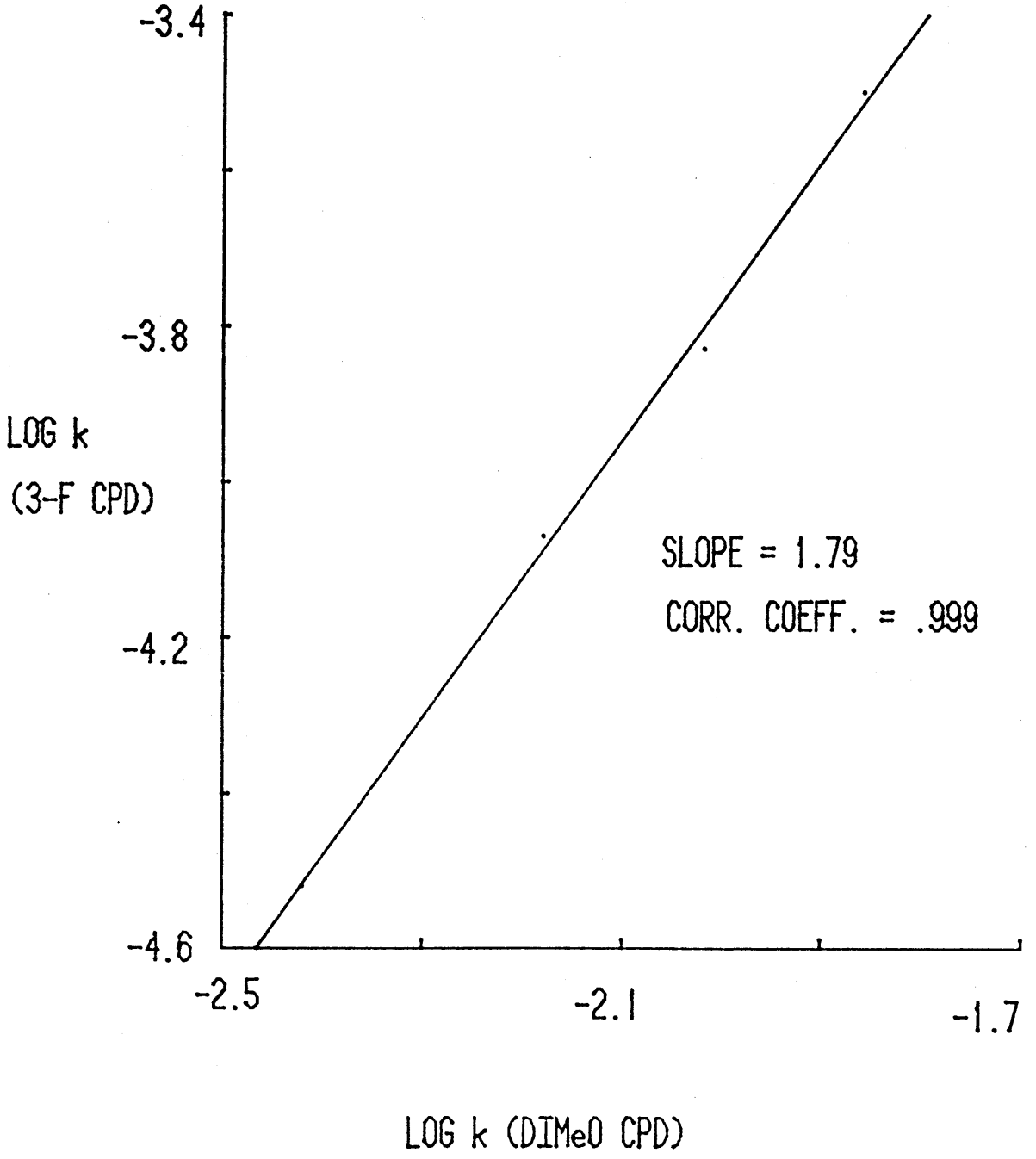
PLOT OF LOG k (3-Me CPD II) VS LOG k (DIMeO CPD XIII)



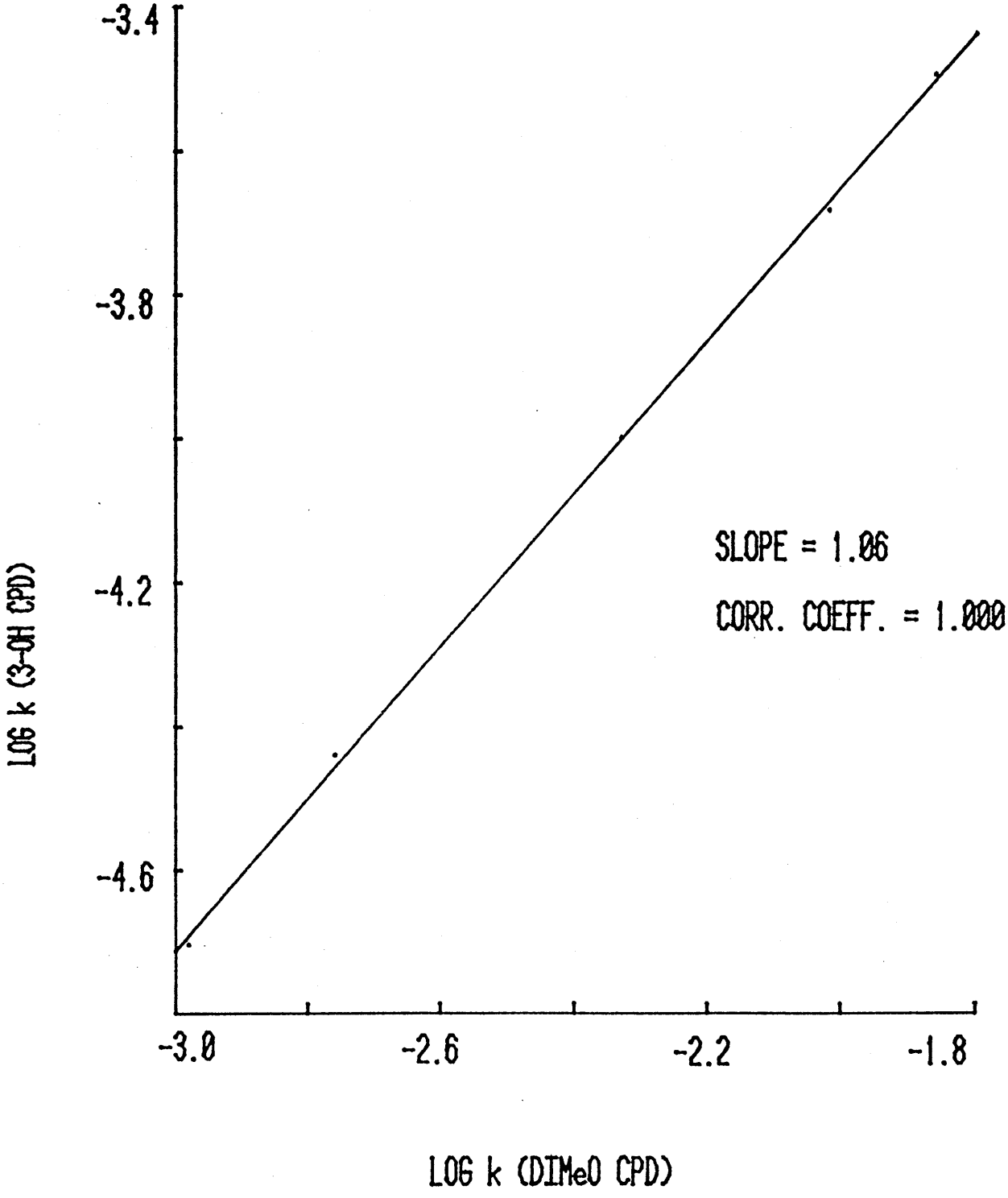
PLOT OF LOG k (3-MeO CPD III) VS LOG k (DIMeO CPD XIII)



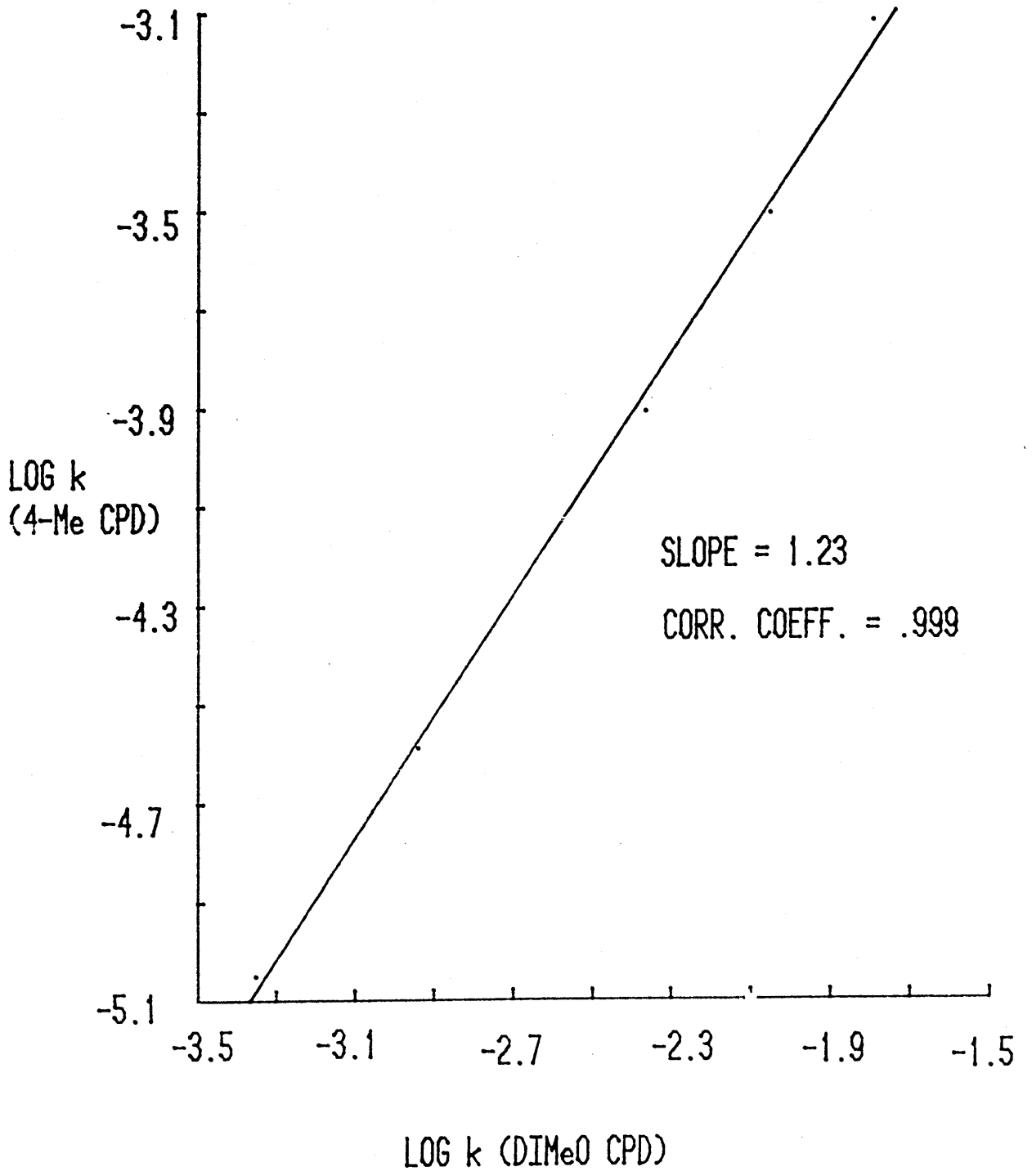
PLOT OF LOG k (3-F CPD V) VS LOG k (DIMeO CPD XIII)



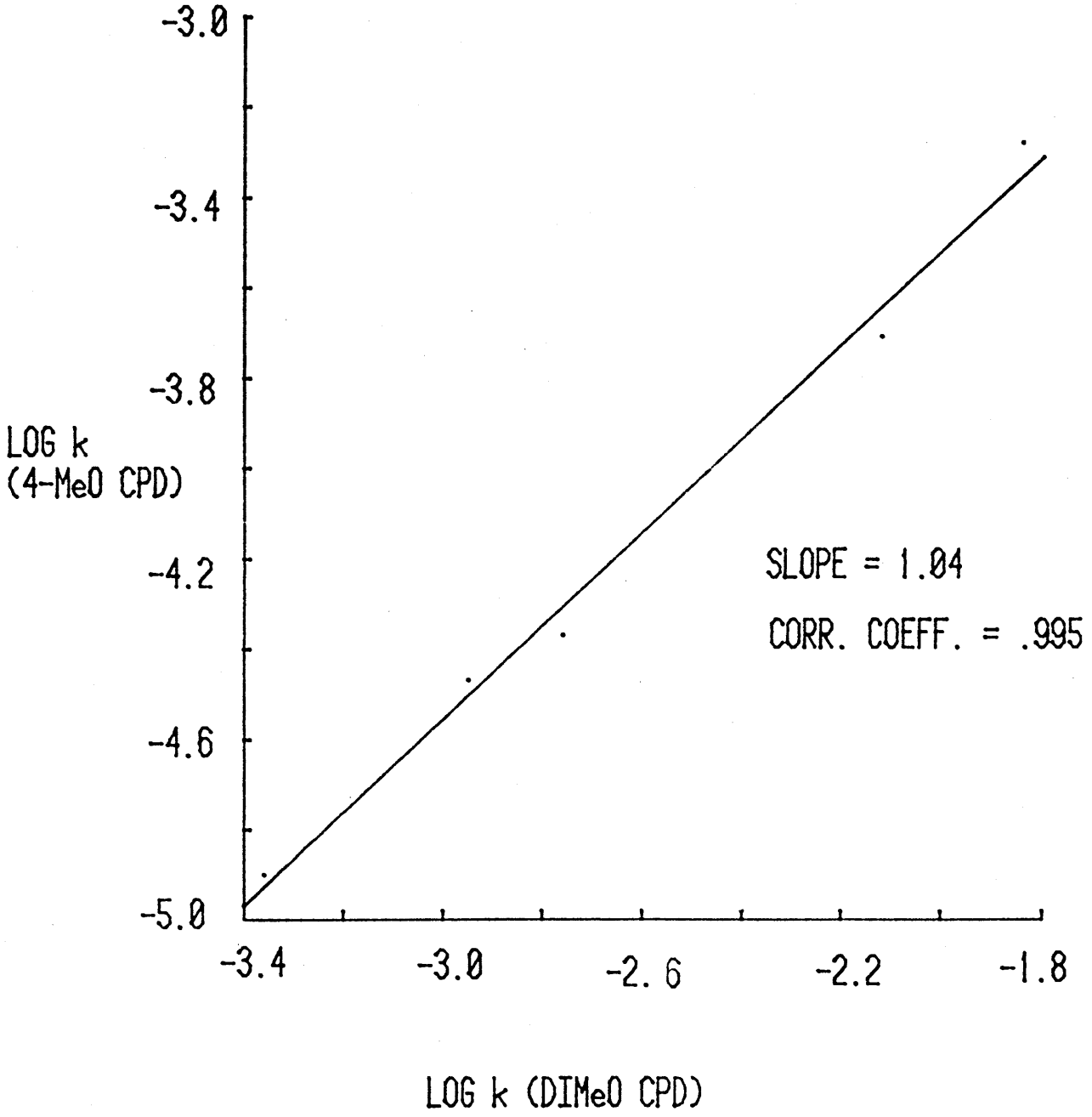
PLOT OF LOG k (3-OH CPD VI) VS LOG k (DIMeO CPD XIII)



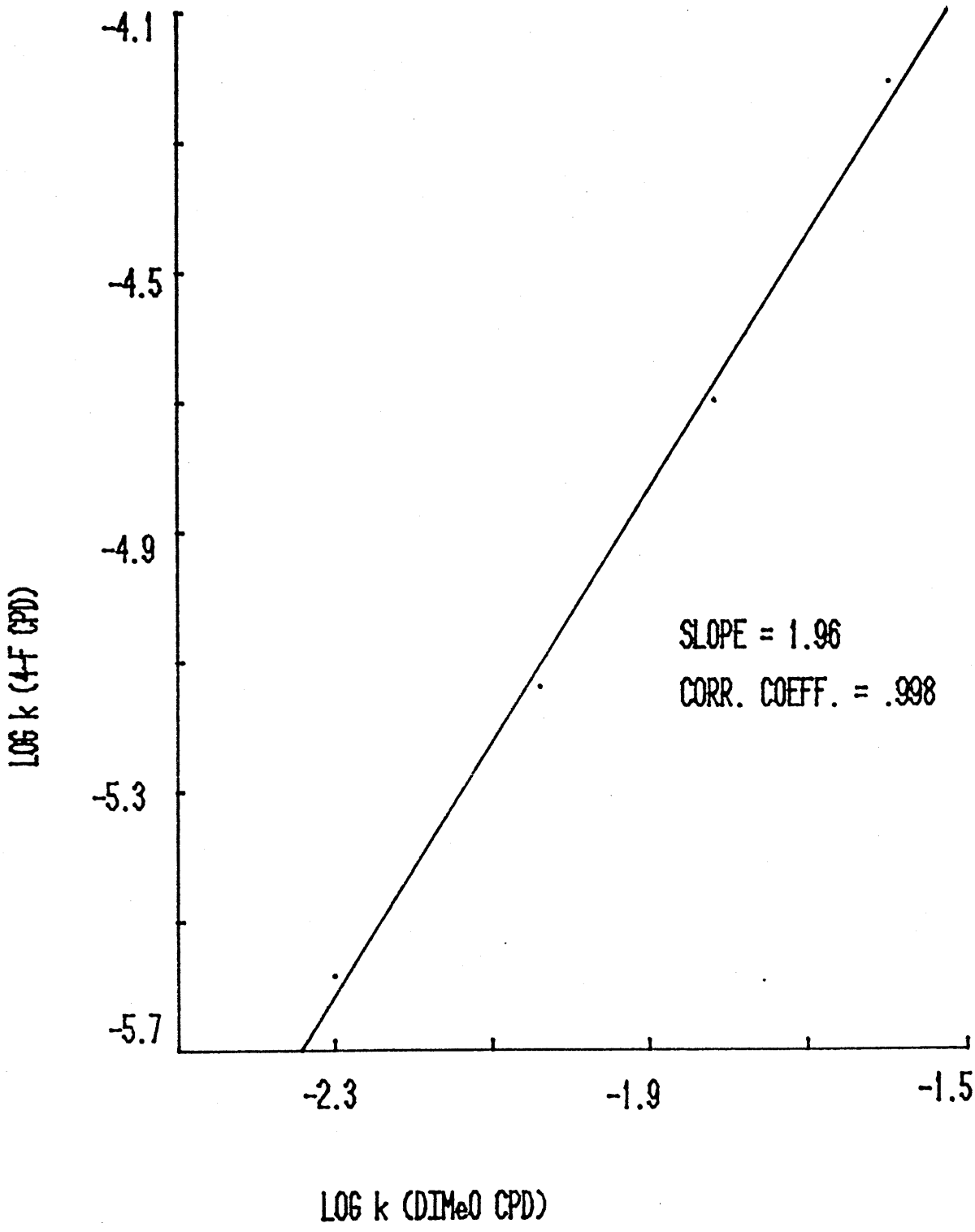
PLOT OF LOG k (4-Me CPD VII) VS LOG k (DIMeO CPD XIII)



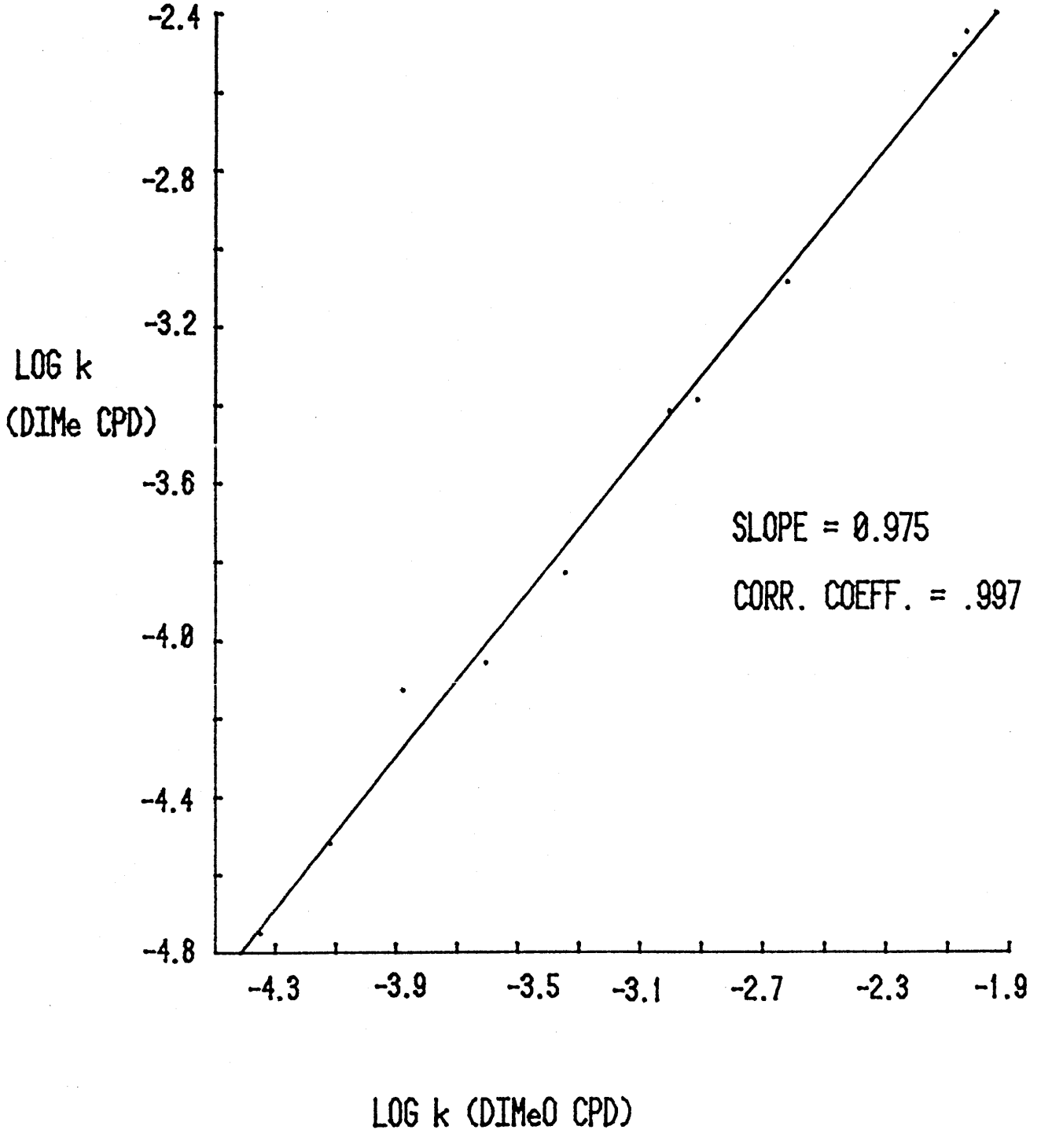
PLOT OF LOG k (4-MeO CPD VIII) VS LOG k (DIMeO CPD XIII)



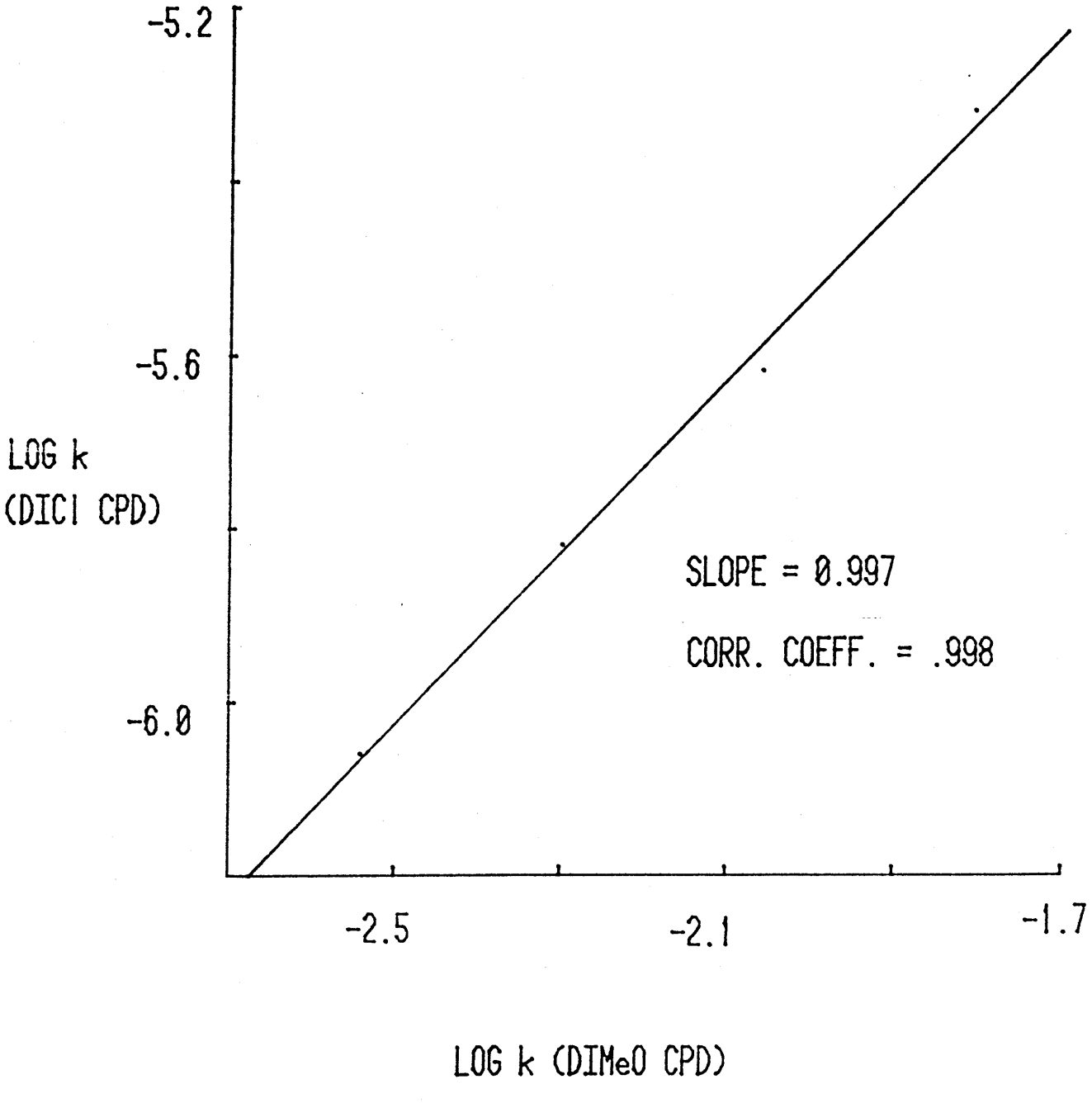
PLOT OF LOG k (4-F CPD X) VS LOG k (DIMeO CPD XIII)



PLOT OF LOG k (DIMe CPD XII) VS LOG k (DIMeO CPD XIII)



PLOT OF LOG k (DICl CPD XIV) VS LOG k (DIMeO CPD XIII)



PLOT OF LOG k (DIPh CPD XV) VS LOG k (DIMeO CPD XIII)

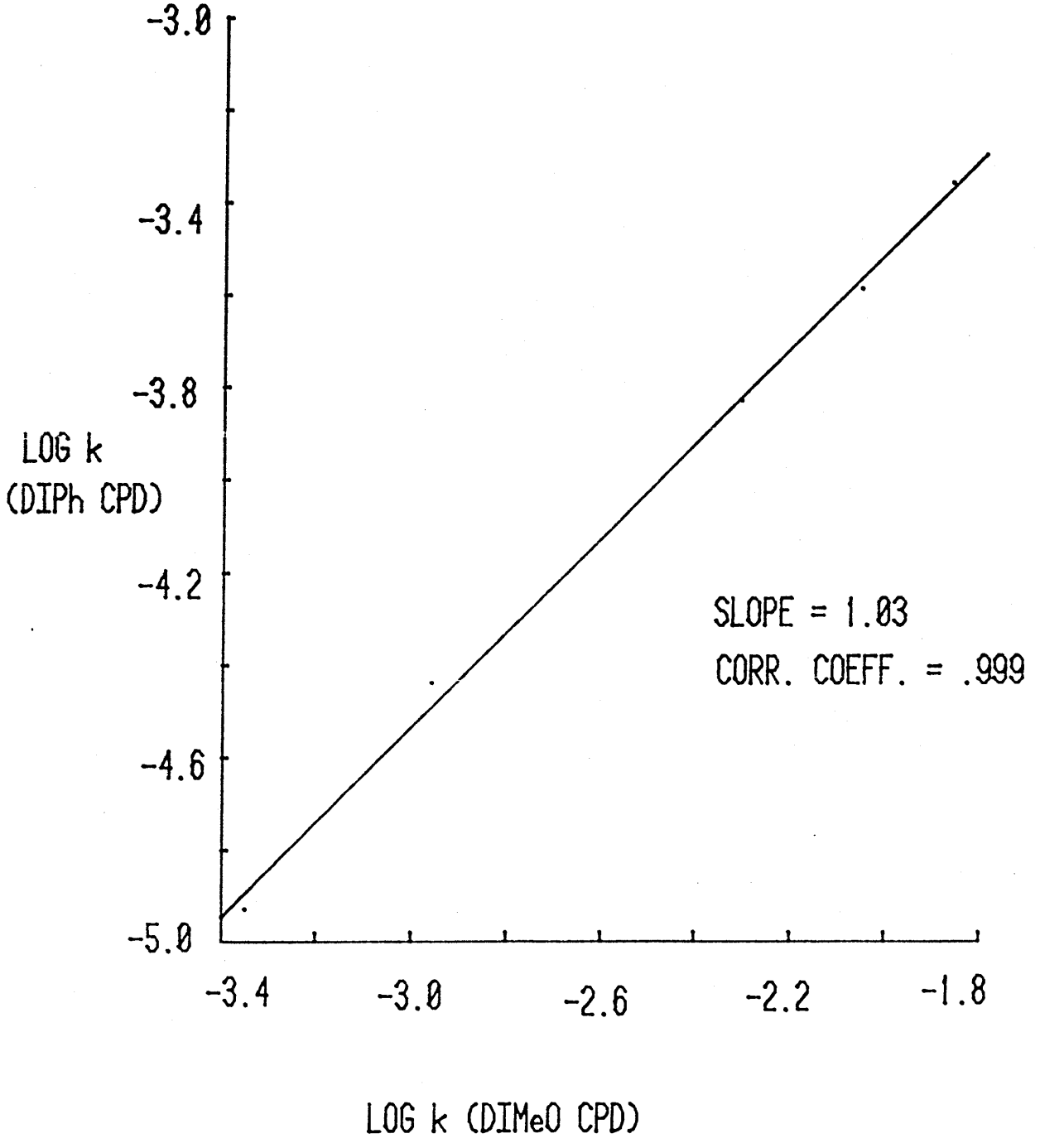


Table 3.43 Data on plots of log k vs H_o (methanesulphonic acid) for the cyclisation of 2-benzylbenzaldehydes

Compound	slope/H_o	Corr. Coeff.	No. of Points
2-Benzylbenzaldehyde	-0.85	0.99	8
2(3-Tolyl)benzaldehyde	-1.05	0.99	5
2(3-Chlorobenzyl)benzaldehyde	-1.18	0.98	6
2(3-Fluorobenzyl)benzaldehyde	-0.79	0.99	8
2(4-Methoxybenzyl)benzaldehyde	-1.15	0.99	5
2(4-Tolyl)benzaldehyde	-0.85	0.99	8
2(4-Fluorobenzyl)benzaldehyde	-1.10	0.99	5
2(4-Chlorobenzyl)benzaldehyde	-1.13	0.99	6

Any correlation with acidity function data in strong aqueous acids of greater than 90% w/w acid strength must be treated with some suspicion. This is because the rapidly decreasing concentration of water may lead to specific medium effects on the activity coefficients of the various species present. This may lead to quite dramatic variation in the slopes of log k vs H_o. However, since the corresponding benzylbenzaldehyde series which are structurally similar are reasonably well behaved in this acid region (Table 3.43) it is doubtful whether this large steady increase of slope with electron withdrawing group ability could be attributed solely to medium effects, although this cannot be ruled out.

It is interesting to note that when log k is plotted against the H_o data of Bascombe and Bell[22] the slopes are considerably lower than

those obtained from combining the data of Bascombe[22] and Paul[23] (Table 3.42). For example the slope for 2(3-tolyl)benzoic acid is reduced from 1.61 to 1.32. This difference becomes larger for compounds with higher slopes, for example with 2(3-fluorobenzyl)benzoic acid the slope is reduced from 2.83 to 2.2. Without further information it is difficult to decide which of the H_o data is more precise for these benzylbenzoic acids. This presumably arises because the indicators used by Paul were different to those used by Bascombe et al. in their study.

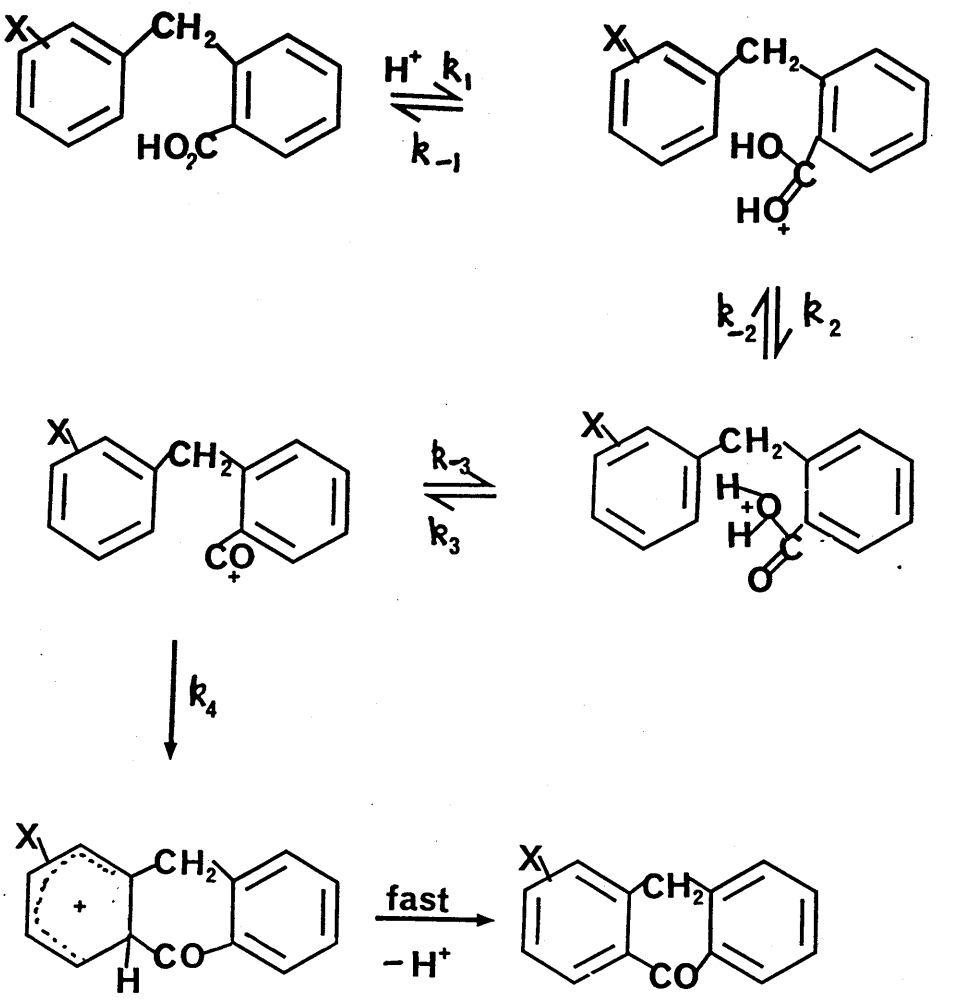
Despite the slight uncertainty in the origin of the variation of the slopes of log k vs H_o it is useful to examine whether the slopes are as would be expected from the proposed mechanism of the reaction and whether the variation in slopes reflect any mechanistic changes.

The proposed mechanism is repeated in Scheme 3.41.

The lack of a kinetic isotope effect shows the last step to be fast and thus the rate limiting step must be between the first and fourth step. Let us consider each in turn.

Case 1 - step 1 rate limiting

This is very unlikely since it is hard to imagine that loss of a proton in the reverse reaction of step 1 could be slower than the forward reaction of step 2 and thus subsequent steps involving cleavage of an O-C bond in step 3 and formation of a C-C bond in step 4. Such proton transfers usually react at the diffusion control rate.



Scheme 3.41

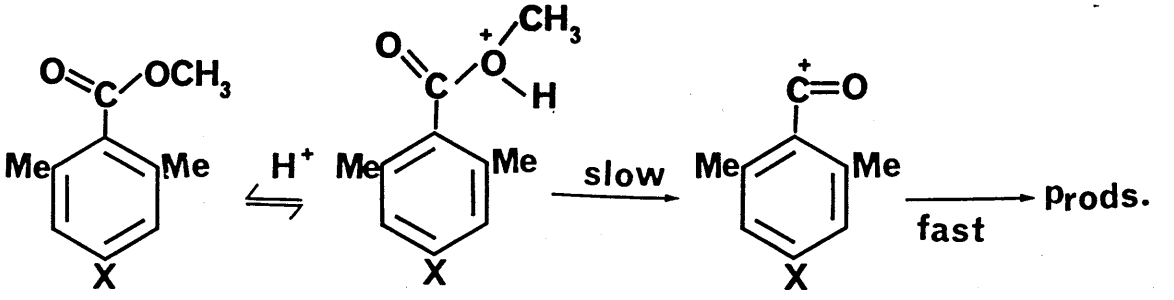
Case 2 - step 2 rate limiting

This again is very unlikely for similar reasons to those given in case 1. Intramolecular proton exchanges such as the reverse of step 2 should be very fast.

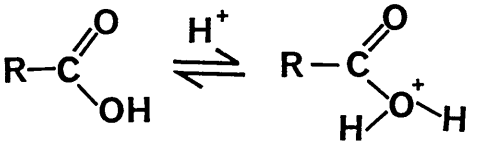
Case 3 - step 3 rate limiting

This would involve the equilibrium formation of the R–C(=O)–O(+)(H)H cation followed by rate limiting loss of a molecule of water. Such a mechanism has been observed in the hydrolysis of esters such as methyl

mesitoate[31,32] where this type of mechanism is promoted by steric hindrance.



pKa data on protonation of the form



are difficult to find in the literature. One possible analogy is with alcohol protonation. Table 3.44 shows some typical data for alcohols.

Table 3.44 pK_a data on alcohols

Alcohol	m[a]	pK_a
Methanol[b]	0.34	-4.86
Ethanol[c]	0.25	-1.94
2-Propanol	0.20	-4.72

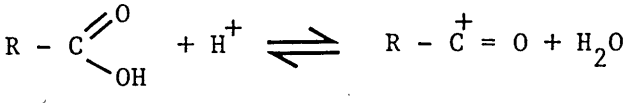
a) As defined in Log I = $mH_o + pK_a$
b) In HCl - R.E. Weston Jr. et al., J. Am. Chem. Soc., 89, 481 (1967).
c) In H_2SO_4 - D.G. Lee and R. Cameron, J. Am. Chem. Soc., 93, 4724 (1971).

For these compounds the plots of log I vs H_o have a very low slope. These low slopes suggest that the increase in solvation which took

place when oxygen bases protonate is greater than that accompanying the protonation of amines (which were used as indicators in the development of the H_o function); i.e. the protonation equilibria for oxygen bases respond less readily to increases in the concentration of mineral acid since each increase in acid concentration is necessarily accompanied by a decrease in the amount of water available to solvate the protonated species. Therefore if this type of equilibrium was the only factor affecting the acidity behaviour of the reaction under study a plot of log k vs H_o should have a small gradient. A similar pattern should also be observed for the hydrolysis of methylmesitoate. However, this is not the case, a plot of log k vs H_o has a gradient of about 1.2.[31] This larger slope could arise for two reasons. Firstly internal solvation by the carbonyl oxygen may occur, thus reducing the increase in solvation on protonation. Secondly in the transition state of the rate limiting step a water molecule is leaving. The activity coefficient of water changes dramatically on increasing the acid strength and this may lead to a higher slope. A more detailed discussion of this appears later.

Case 4 - step 4 rate limiting

This corresponds to the more conventional mechanism for electrophilic aromatic substitution, the equilibrium formation of the electrophile followed by the rate limiting formation of the Wheland intermediate. In this case the acidity behaviour is governed by the equilibrium:



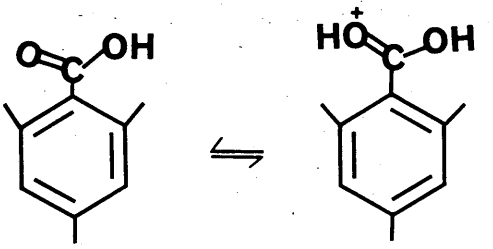
This equilibrium should have a high slope of log I vs H_o since the

activity of water must also be considered. Such a protonation should follow the H_R scale which involves the formation of carbocations from triarylcarbinols

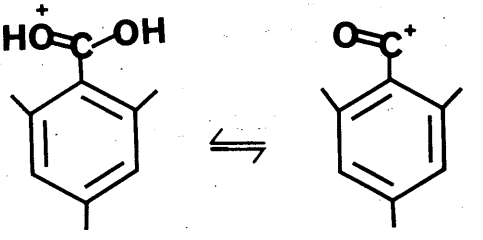
$$R_3\text{-C-OH} + H^+ \rightleftharpoons R_3C^+ + H_2O$$

The H_R scale has a slope against H_o of about 2 although in concentrated acid media where the concentration of water is rapidly diminishing this slope increases to 3 or 4.

Data for the two equilibria shown below in concentrated sulphuric acid are available in the literature[33] (equation 3.40 and 3.40a).



(3.40)



(3.40a)

A combination of the two sets of data shows that a plot of log I vs H_o for the equilibrium represented by equation 3.40a in 90-100% sulphuric acid has a slope of about 3 and thus, as predicted, seems to follow the H_R scale (the slope against H_R is about 1.1).

In conclusion, if the fourth step is rate limiting the reaction under study should give rise to large slopes when log k_{obs} is plotted against

H_o. These slopes will be particularly large, 2-4, considering the strong acid conditions employed in this study.

The Hammett plot obtained using substituents in the benzyl moiety (see section 3.5) indicates that there is a change in rate limiting steps on changing from electron donating to electron withdrawing groups. With electron withdrawing groups the fourth step is thought to be rate limiting whereas with electron donating groups the third step is rate limiting. The slopes of log k vs H_o obtained for the various substituents seem to bear this out.

With electron donating groups the slopes against H_o are about 1.6 - 1.7 in agreement with slopes of greater than unity obtained in the hydrolysis of mesitoate esters which have a similar rate limiting step. If the fourth step were rate limiting for this class of compounds then plots of log k vs H_R should produce a straight line of slope unity. At the present moment this cannot be tested as H_R is not defined for methanesulphonic acid in the range 94-100%. Attempts were made to obtain log I data in this range using three arylcarbinol indicators. Whilst this would not allow absolute calculations of H_R values, it could indicate how H_R varied with % acid in this region. However, in each case the results did not lend themselves to extend the range beyond 94%. It was, however, possible to use this log I data to plot against log k_{obs} for compounds XII and XIII as their cyclisations were carried out in 85-100% methanesulphonic acid.

These graphs (reproduced on pages 197-198) clearly show that these two compounds at least do not follow the H_R acidity function in the range 84-90% methanesulphonic acid. The two slopes against log I being 0.55 and 0.535 respectively. Thus it seems that for compounds with a lower

slope the loss of water in the third step becomes rate limiting. In this case the water does not compete successfully with the benzyl moiety for the carboxonium ion. With the more reactive aromatics the carboxonium ion reacts to give the product as soon as the carboxonium ion is formed in the third step. If the loss of water to form the carboxonium ion is rate limiting the slope against H_o should be considerably less than if this step was a pre-equilibrium. Writing the mechanism in a reduced fashion

$$S + H^+ \overset{K}{\rightleftharpoons} SH^+ \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} S^+ + H_2O \xrightarrow{k_2} \text{Products}$$

From transition state theory

$$k_{obs} = K^{\ominus} k_1^{\ominus} . (f_S f_{H^+} / f_1^{\neq}) [H^+] \qquad (3.41)$$

$$\log k_{obs} = \log K^{\ominus} k_1^{\ominus} + \log a_{H^+} + \log f_S / f_1^{\neq}$$

$$\text{since } H_o = -\log a_{H^+} - \log (f_B / f_{BH^+})$$

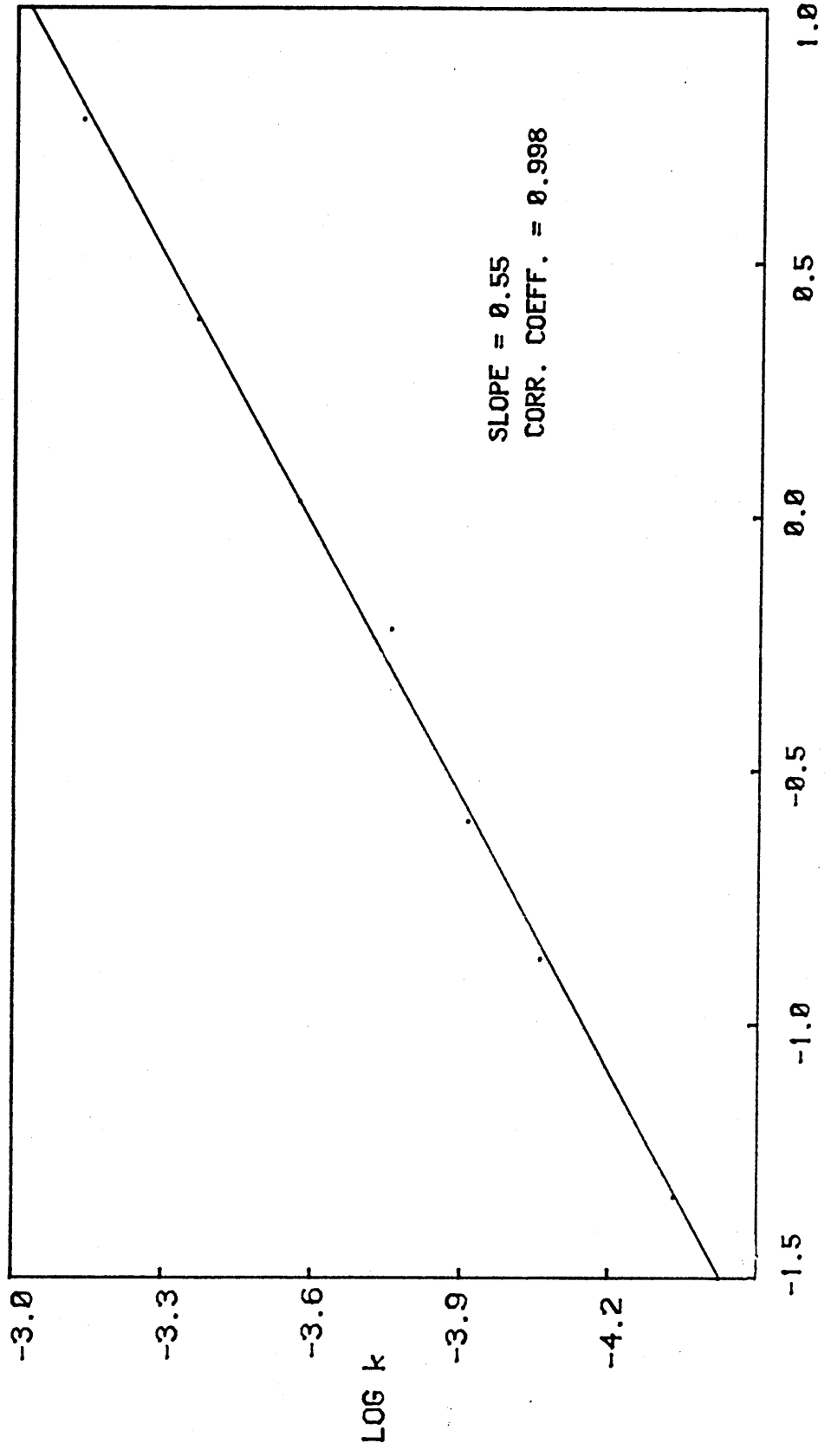
$$\log k_{obs} = \log K^{\ominus} k_1^{\ominus} - H_o + \log (f_S f_{BH^+} / f_B f_1^{\neq}) \qquad (3.42)$$

B = Hammett base

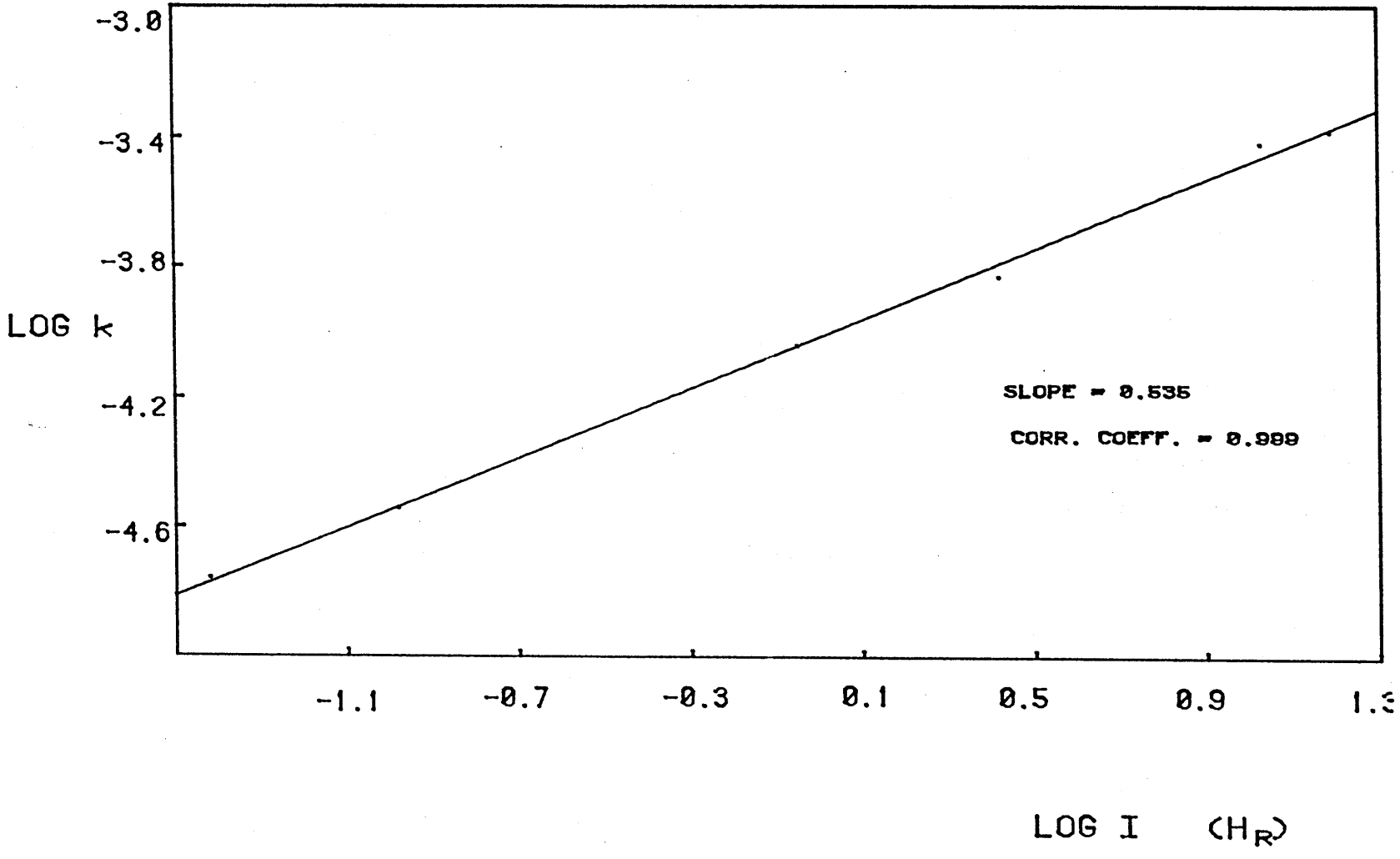
Deviation from a slope of 1 arise because of differences in the activity coefficient ratios between f_B and f_{BH^+} and f_S and $f_1^{\neq}$.

It is possible to estimate qualitatively the size of this activity coefficient ratio. The transition state involves the partial formation of a carbonium ion and loss of a molecule of water and this reflects, although in a diminished form, changes in the activity coefficients of

PLOT OF LOG I (H_R) VS LOG k FOR DIMeO CPD (XIII)



PLOT OF LOG I (H_R) VS LOG k FOR DIMe CPD (XII)



the fully formed species. Subtraction of the expressions for H_o and H_R gives

$$H_R - H_o = \log [H_2O] - \log (f_S\, f_{BH}^{+}/f_B f_{H_2O} f_{S^+}) \qquad (3.43)$$

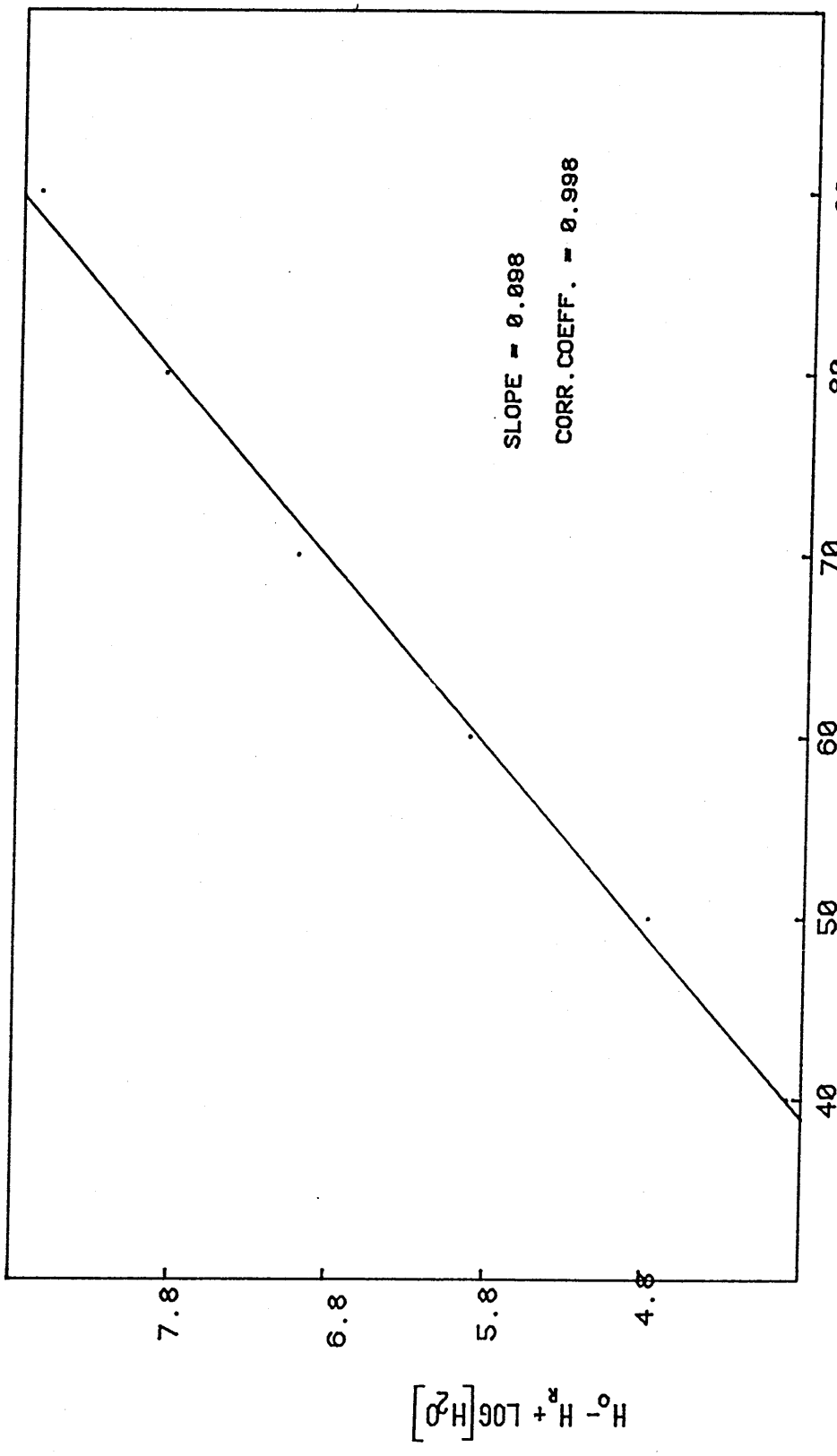
where $S = ArC\text{-}OH$

$S^+ = Ar_3C^+$

Thus a plot of $H_o - H_R + \log [H_2O]$ against % acid should show how this latter activity coefficient ratio term varies with acid strength. Figure 3.42 shows the relevant plot and it is therefore not surprising that, if the activity coefficient term in equation 3.42 resembles in a reduced way that of equation 3.43, the gradient of log k vs H_o for the reaction under study will be greater than unity.

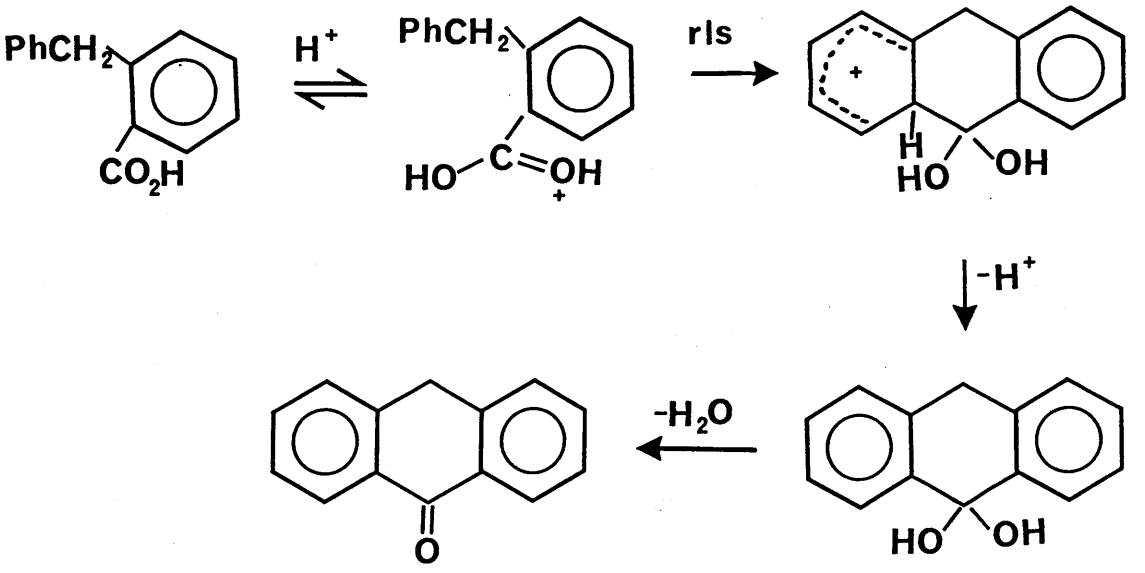
With electron withdrawing groups the slopes of log k against H_o are very large; about 3. In this case the rates seem to follow H_R as did the equilibrium for carboxonium ion formation with mesitoic acid.

This suggests that in this case the fourth step is rate limiting and the protonation of the benzylbenzoic acid and subsequent loss of water and carboxonium ion formation are an established pre-equilibrium. In this case water competes successfully with the benzyl moiety for reaction with the carboxonium ion.


PLOT OF $H_o - H_R + LOG[H_2O]$ VS % H_2SO_4
SLOPE = 0.098
CORR.COEFF. = 0.998
$H_o - H_R + LOG[H_2O]$
7.8
6.8
5.8
4.8
40
50
60
70
80
90
% H_2SO_4

(FIG. 3.42)

The lower slopes of log k against H_o could also be produced if there was a change in mechanism and the protonated carbonium ion acted as the electrophile for the activated benzyl compounds (Scheme 3.42).



Scheme 3.42

From transition state theory;

$$k_{obs} = K^{\ominus}k_1^{\ominus}.(f_S f_{H^+}/f_1^{\neq})[H^+]$$

and again,

$$\log k_{obs} = \log K^{\ominus}k_1^{\ominus} - H_o + \log (f_S f_{BH^+}/f_B f_1^{\neq})$$

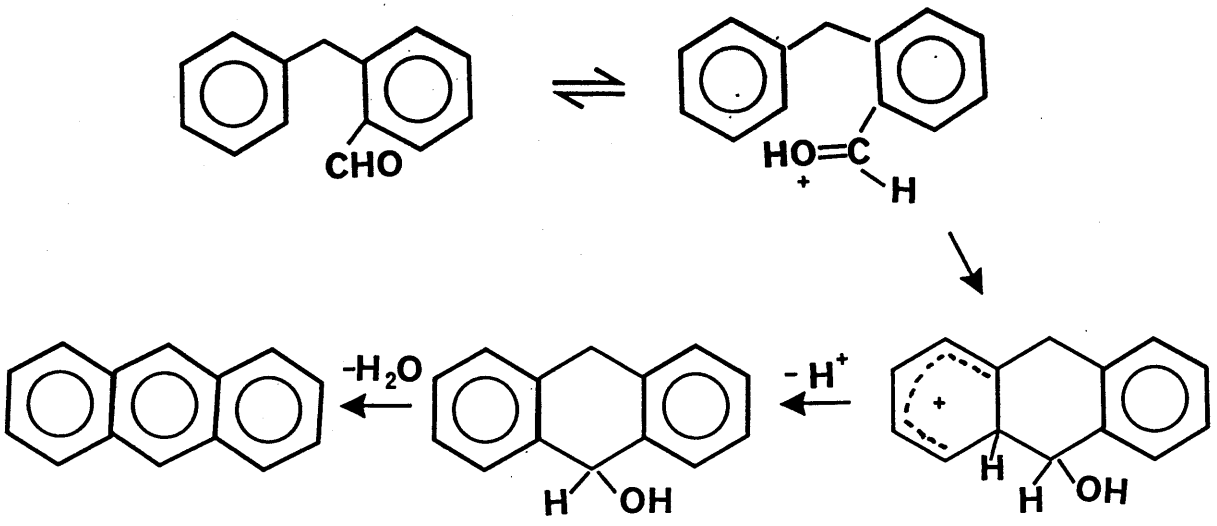
In this case if the variation in the activity coefficient of the transition state reflects that of the protonated carbonyl species a low slope of log k vs H_o might be expected (Table 3.45). Although, the value for m for mesitoic acid is one of the larger values.

Table 3.45 Slopes of Log I vs H_o and pK_a for various carbonyl compounds

Compound	m^a	$-pK_a$
Benzaldehyde	0.53	3.54
4-Methylbenzaldehyde	0.61	4.16
Acetophenone	0.63	4.03
Benzophenone	0.71	4.74
Anthraquinone	0.94	8.08
Benzoic acid	0.58	4.39
Cinnamic acid	0.58	3.99
Ethylbenzoate	0.74	5.94
Benzamide	0.60	1.55
Cinnamide	0.66	1.21
Mesitoic acid	0.89	7.3

a - As defined in Log I = $mH_o + pK_a$

In fact this mechanism is analogous to that obtained for 2-benzylbenzaldehydes (Scheme 3.43) which had slopes against H_o of 0.85 - 1.1 (Table 3.43), confirming that the slopes are not necessarily small.



Scheme 3.43

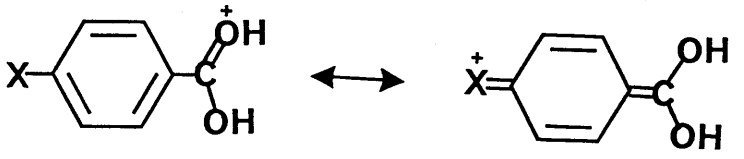
Evidence against this second mechanism is presented in the next section.

Before discussing the Hammett plots for this system, it is useful to speculate on the possible pKa's of these benzylbenzoic acids. Since, in all cases, the rate increases linearly with H_o there is no evidence of protonation to greater than 10%. If protonation of the substrate did occur to a large degree the rate would level off as most of the substrate would be in the conjugate acid form and increasing the acidity would not significantly increase its concentration. This behaviour is observed at about 95% sulphuric acid for the cyclodehydration of benzoylbenzoic acids.[34] This indicates that the H_o for half protonation ($H_o^{\frac{1}{2}}$) of these acids is greater than -7.8. $H_o^{\frac{1}{2}}$ for benzoic acid occurs around -7.4 which would mean that it would be 50% protonated in 95% methanesulphonic acid. $H_o^{\frac{1}{2}}$ for some substituted benzoic acids are given in Table 3.46.

Table 3.46 $H_o^{\frac{1}{2}}$ for substituted benzoic acids

Substituent	$H_o^{\frac{1}{2}}$
H	-7.4
3-Me	-7.2
4-Me	-6.92
4-Et	-6.92

The reason why the $H_o^{\frac{1}{2}}$ of these substituted benzylbenzoic acids are more negative than expected is a result of steric inhibition to conjugation. A similar behaviour is observed for mesitoic acid which, despite the presence of three electron donating groups has an $H_o^{\frac{1}{2}}$ of -7.85. In this case the two ortho methyl groups flanking the carboxylic acid group keep the plane of the -C-OH group at right angles to the plane of the phenyl ring. This prevents any conjugation with the aromatic system. Thus there is no stabilisation of the conjugate acid from resonance canonicals of the form



This leads to a more negative pKa and $H_o^{\frac{1}{2}}$.

3.5 Application of the Hammett Equation

The Hammett equation (3.51) was used in the interpretation of the experimental results.

$$\log k = \sigma\rho + \log k_o \qquad (3.51)$$

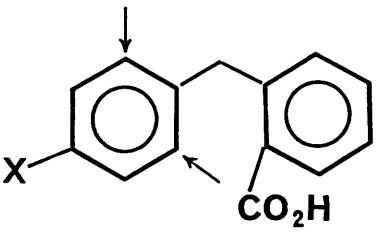
In aromatic electrophilic substitutions ρ is indicative of the amount of positive charge delocalised in the aromatic nucleus in the transition state. Very large negative ρ values indicate that the transition state resembles a σ-complex. Table 3.51 gives ρ values for a number of aromatic electrophilic substitutions. From this data ethylation for instance would have a more reactant like transition state than chlorination or bromination.

Table 3.51 ρ values for some aromatic electrophilic substitutions

Reaction	ρ
Nitration	-6.0
Ethylation	-2.4
Acetylation	-9.1
Chlorination	-10.0
Bromination	-12.1

In this project plots were made of log k against both σ and σ^+. However, σ^+ values were chosen because in many electrophilic substitutions where attack takes place directly on the aromatic a good correlation with σ is not obtained. These are situations where the substituent can enter into direct conjugation with the reaction site in the transition state. H.C. Brown devised σ^+ values in order to overcome these difficulties. All the log k data used was at 97%

methanesulphonic acid. This was mainly because log k was available at this figure for all the benzylbenzoic acids studied. Values at 100% methanesulphonic acid could not be used as they were sometimes unreliable and did not correlate well with the rest of the kinetic data. In a number of the benzylbenzoic acids two identical positions of attack were available (3.52) and this statistical factor has been taken into account in the calculation of log k values.



(3.52)

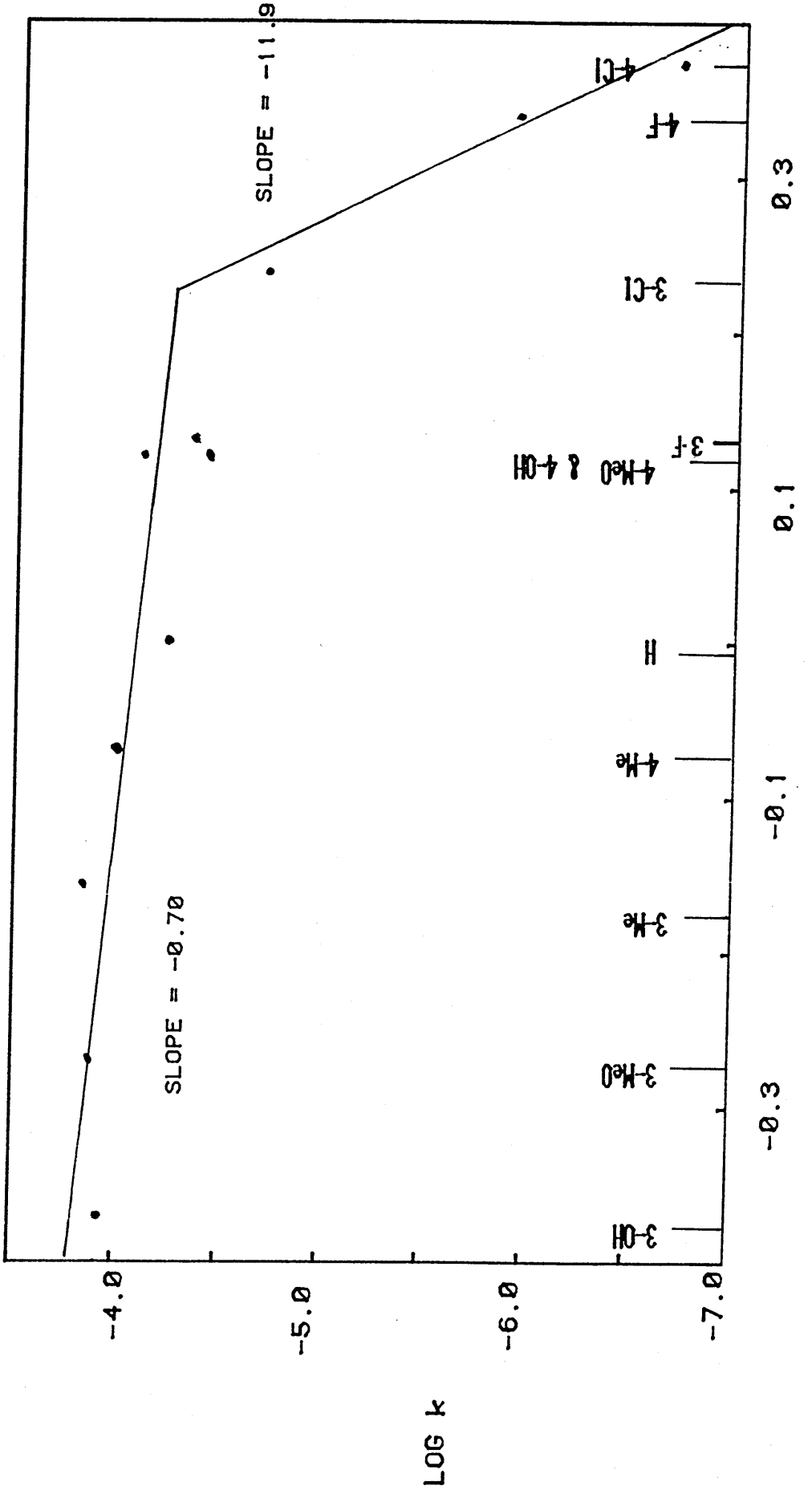
In this compound two identical positions are present at which electrophilic attack can take place, both are meta to the substituent.

The two graphs obtained are shown in Figures 3.51 and 3.52. In both cases similar results were obtained.

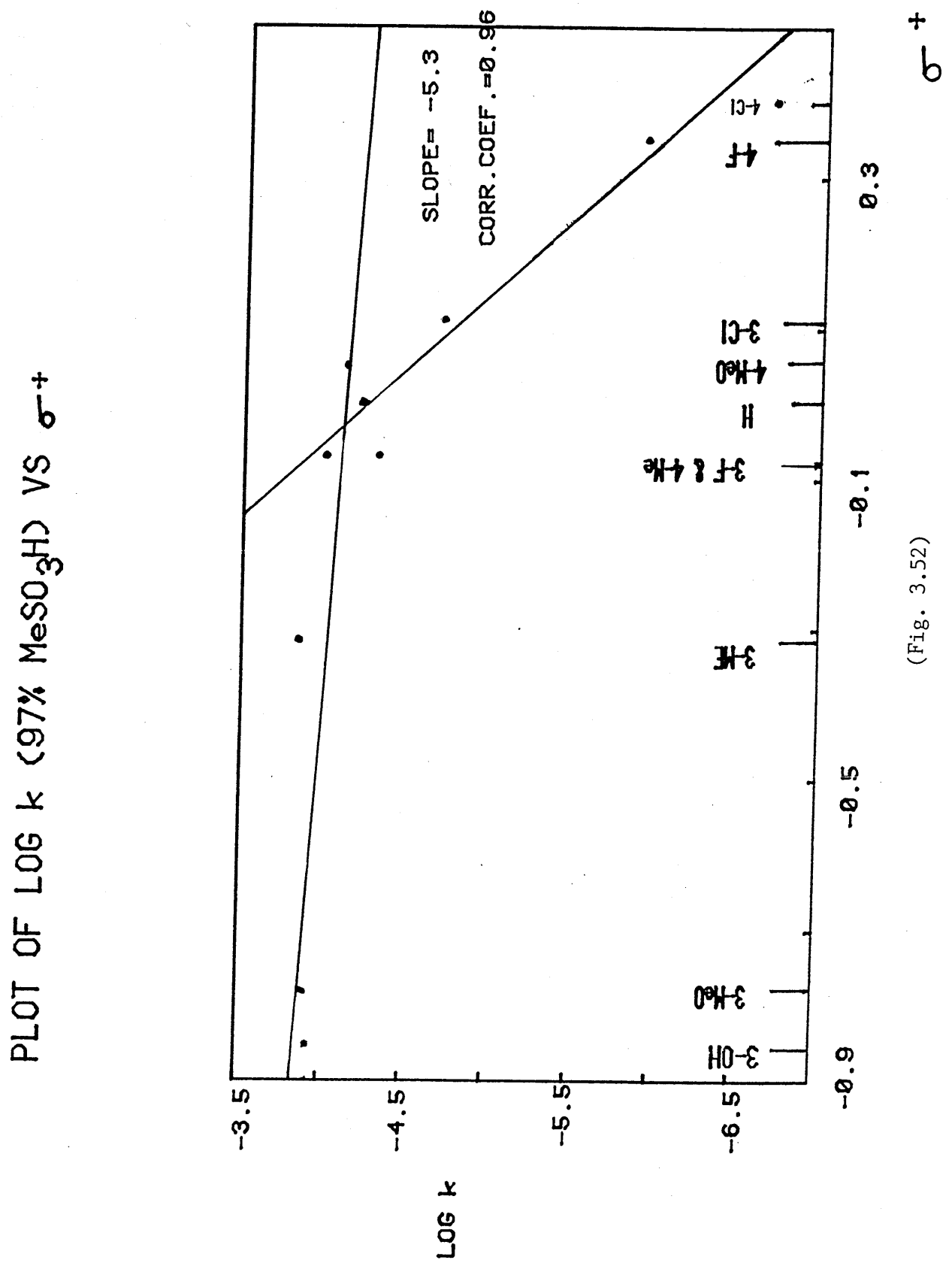
Considerable curvature is seen in these graphs and this is indicative of a change in the rate determining step. Consider the last mechanism proposed in Scheme 3.51 where S represents a benzylbenzoic acid and P the products of cyclodehydration.

$$S + H^+ \overset{K}{\rightleftharpoons} SH^+ \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} S^+ + H_2O \xrightarrow{k_2} P$$

Scheme 3.51


PLOT OF LOG k (97% MeSO3H) VS σ
SLOPE = -11.9
SLOPE = -0.70
LOG k
-4.0
-5.0
-6.0
-7.0
σ
0.3
0.1
-0.1
-0.3
4-Cl
4-F
3-Cl
3-F
4-MeO & 4-OH
H
4-Me
3-Me
3-MeO
3-OH

(Fig. 3.51)


PLOT OF LOG k (97% MeSO3H) VS σ+
SLOPE= -5.3
CORR.COEF.=0.96
LOG k
-3.5
-4.5
-5.5
-6.5
-0.9
-0.5
-0.1
0.3
σ+
3-OH
3-MeO
3-ME
3-F & 4-Me
H
4-MeO
3-Cl
4-F
4-Cl

(Fig. 3.52)

Here

$$d[P]/dt = k_2[S^+] \tag{3.53}$$

and

$$d[S^+]/dt = k_1[SH^+] - [k_{-1}[H_2O]+k_2]\ [S^+] \tag{3.54}$$

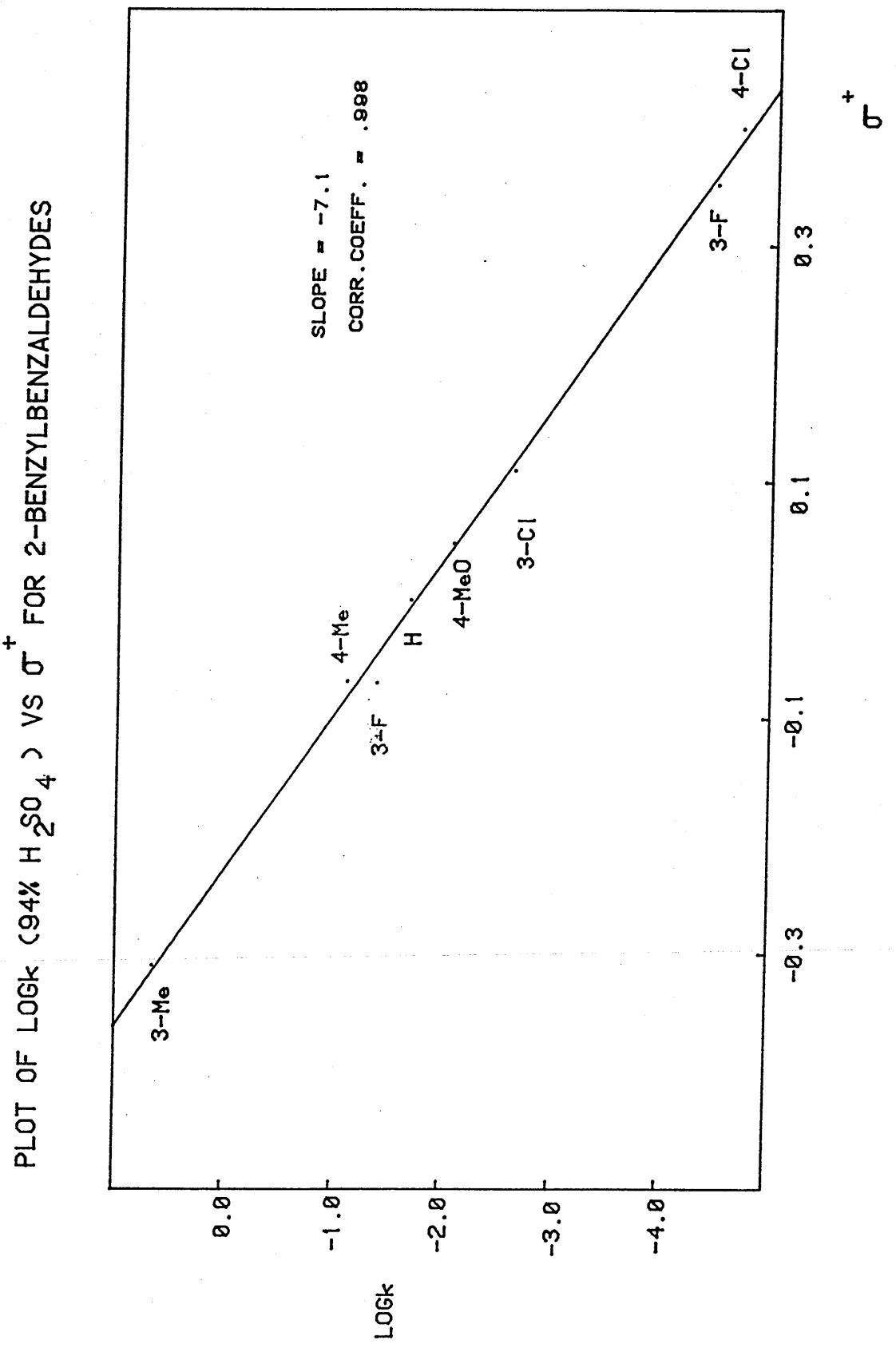
By applying the steady state assumption

$$[S^+] = k_1[SH^+]/(k_{-1}[H_2O] + k_2) \tag{3.55}$$

$$d[P]/dt = k_2k_1[SH^+]/(k_{-1}[H_2O] + k_2) \tag{3.56}$$

$$= k_2k_1K[S][H^+]/(k_{-1}[H_2O] + k_2)$$

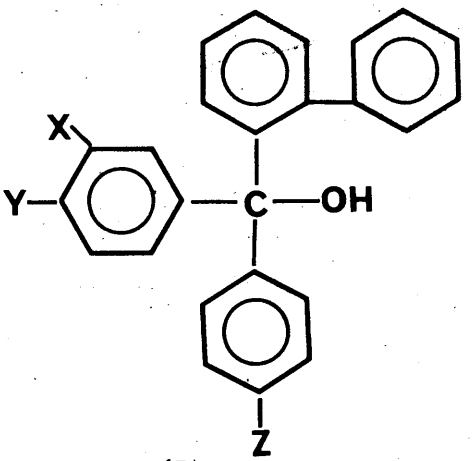
In a situation where $k_2 < k_{-1}\ [H_2O]$, i.e. where the second step is a pre-equilibrium and the last step is rate limiting, the rate depends on the reactivity of the benzyl moiety and a good Hammett plot should be obtained with a relatively large slope. In this case since the second pre-equilibrium step involves loss of water, a large slope should be observed in a plot of log k against % methanesulphonic acid, and the reaction should correlate with H_R as discussed earlier. This is found to be so when the benzyl ring contains electron withdrawing groups such as Cl and F. A ρ value of -5.3 against σ^+ was obtained using these substituents which is reasonable for an electrophilic substitution and is comparable to that of nitration and also the cyclodehydration of 2-benzylbenzaldehydes,[35] which has a ρ value of -7.1 (Figure 3.53).


PLOT OF LOGk (94% H_2SO_4) VS σ^+ FOR 2-BENZYLBENZALDEHYDES
SLOPE = -7.1
CORR.COEFF. = .998
3-Me
4-Me
3-F
H
4-MeO
3-Cl
3-F
4-Cl
LOGk
0.0
-1.0
-2.0
-3.0
-4.0
-0.3
-0.1
0.1
0.3
σ^+

(FIG. 3.53)

Where $k_2 > k_{-1}[H_2O]$, step 3 is rate limiting. Here, since k_2 is not involved in the rate equation, the rate no longer depends on the reactivity of the benzyl moiety and therefore a Hammett plot would not be expected to show a large slope (<1). The slope expected from a plot of log k, against % methanesulphonic acid would also be lower than in the previous case as discussed earlier. This is found to be so when electron donating groups are present in the benzyl ring. The ρ value obtained for these compounds is close to 0.

A cyclodehydration reaction where a similar changeover in the rate limiting step was observed has been studied by H. Hart and E. Sedor.[36] They cyclised 2-phenyltriarylcarbinols (I) in the presence of 80% aqueous ethanoic acid containing 4% sulphuric acid at 25°C.



(I)

The Hammett plot they obtained from their kinetic studies was a composite of two straight lines with a sharp concave downward break (Figure 3.54).

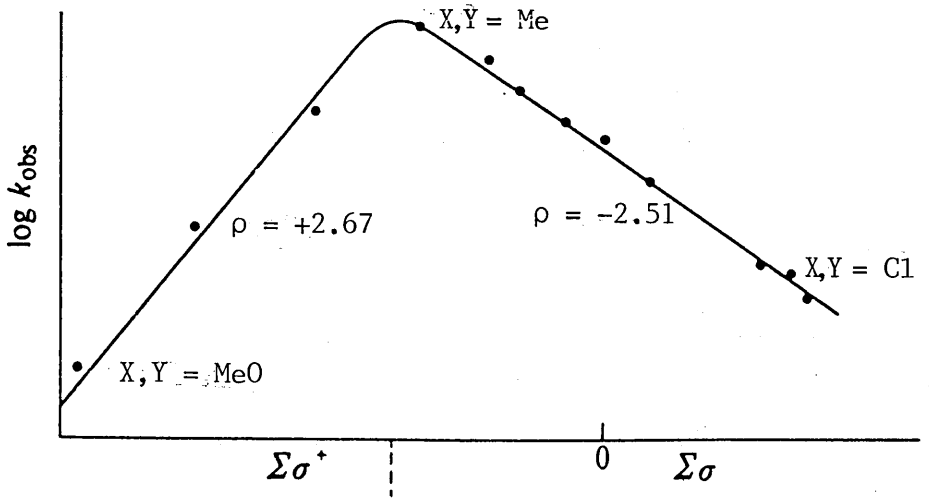
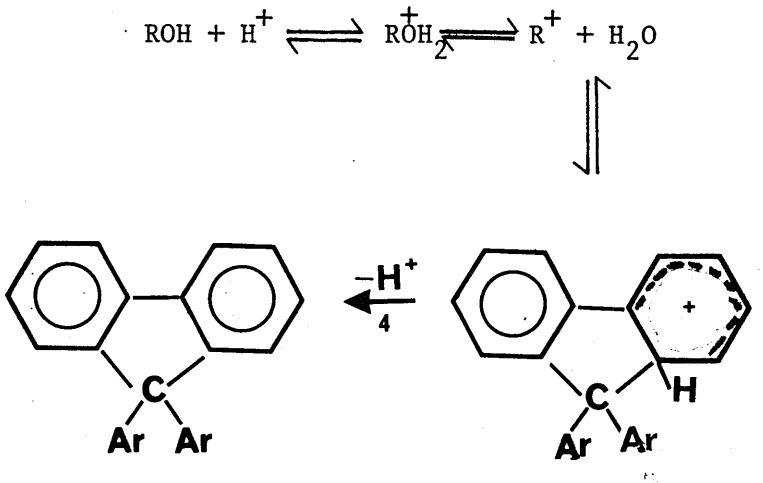


Figure 3.54

This type of Hammett plot is indicative of a common mechanism that has different rate limiting steps.[37] The mechanism proposed for this reaction follows a four step pathway (Scheme 3.52).

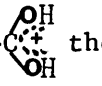
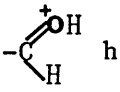


Scheme 3.52

ROH = 2-phenyltriarylcarbinol

They proposed that on the right hand side of the Hammett plot in Fig. 3.54 a negative value is obtained which indicates a build up of positive charge in the rate limiting step and therefore step 2 in scheme 3.52 is probably rate limiting. This series of compounds contains substituents such as Cl, CF_3 and Me.

The left hand side of the Hammett plot in Fig. 3.54 has a ρ value of +2.67. In this case therefore there is a decrease in positive charge at the reaction centre during the rate limiting step and consequently step 3 (Scheme 3.52) should be rate limiting. This series of compounds contain only OMe groups which are able to stabilise the R^+ carbonium ion such that most of the substrate exists in this form and the rates correlate better with σ^+ than with σ.

The second possible mechanism proposed in Scheme 3.42 would not generate this type of curved Hammett plot. Whilst the two ρ values would be different for the two electrophiles $-C^+=O$ and  the latter would not be expected to have a value close to 0. As mentioned earlier the analogous electrophile  had a ρ value of -7.1. Thus this change in mechanism should generate a much smaller discontinuity and can therefore be discounted.

The insensitivity of the rate constants to changes in substituent for electron donating groups is also not a result of protonation of the benzyl ring. If the benzyl ring were substantially protonated in this media then increasing the acid strength would have little effect on the rate since reaction could occur on the minor free base form of the benzyl ring. The Hammett plot would also level off due to compensation between the change in reactivity and the pKa. However $H_o^{\frac{1}{2}}$ for ring protonation of 3,5-dimethoxytoluene has been calculated to be about -6.3 (90% methanesulphonic acid)[38] so it is very doubtful whether any of the substrates under consideration would be substantially protonated under the conditions of this study. This is also borne out by results from the benzylbenzaldehyde series where no such levelling off is apparent despite the presence of identical benzyl moieties.

It is possible that the methoxy oxygen could be protonated in methanesulphonic acid, therefore reducing the reactivity of the ring towards electrophilic substitution. In sulphuric acid of similar strength (H_o) nitration studies have been carried out on anisoles by Barnett et al.[38] This study shows that when log k_2 is plotted against wt% sulphuric acid a straight line is obtained for anisole and o- and p-methylanisoles, the slope being the same as that of mesitylene. In this region the products from o- and p-methylanisole are in constant ratio indicating no evidence for the protonation of the methoxy oxygen. The nitration products for anisole do vary a little in this region, but this is thought to be due to changes in degree of hydrogen bonding. Moodie et al. have carried out nitration studies on anisole in 80 - 97% methanesulphonic acid.[39] Here the anisole behaves as would be expected at encounter rate and again there was no evidence for the protonation of the methoxy oxygen. There was no evidence of demethylation of the 2(3-methoxy benzyl)benzoic acid on cyclodehydration as may have been expected if ring protonation was substantial. The formation of a complex between the electrophile or potential electrophile and the methoxy group can also be discounted on considering a model of the molecule.

It is curious that the 4-methoxysubstituent which has a positive σ^+ value is more reactive than the unsubstituted compound, whereas the 3-fluoro substituent which has a negative σ^+ value is less reactive. Indeed despite only a small reactivity difference between these two compounds there seems to be a clear difference in the rate limiting step, as determined by the slope of log k vs H_o. Clearly other factors affect the relative rate of attack of the electrophile by H_2O and the benzyl moiety such that the distinction is not clear cut. The unsubstituted compound has an intermediate slope of log k vs H_o and it

was hoped that in this instance a transition from the third step being rate limiting to the 2nd being rate limiting would be observed as the acid concentration increased and the concentration of water decreased. This would manifest itself by a decrease in the slope of log k vs H_o as the acid concentration increased. However, no such trend was observed.

The presence of substituents in the benzoic acid ring have little effect on the slopes of log k against H_o (see Table 3.42). This is because the key feature is the reactivity of the benzyl ring with respect to water, i.e. k_{-1} $[H_2O]$: k_2. As there is an electron donating group present in the benzyl ring in all compounds with substituents in the benzoic acid ring k_2 will be greater that k_{-1} $[H_2O]$ and k_1 is rate limiting. A Hammett plot using the substituents in the benzoic acid ring is given in Figure 3.55. Here the σ values of the two substituents have been added together. σ^+ values were used in preference to σ due to the likelihood of through-conjugation with the electrophile (Figure 3.56).

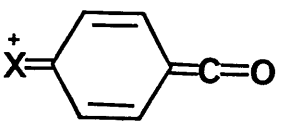
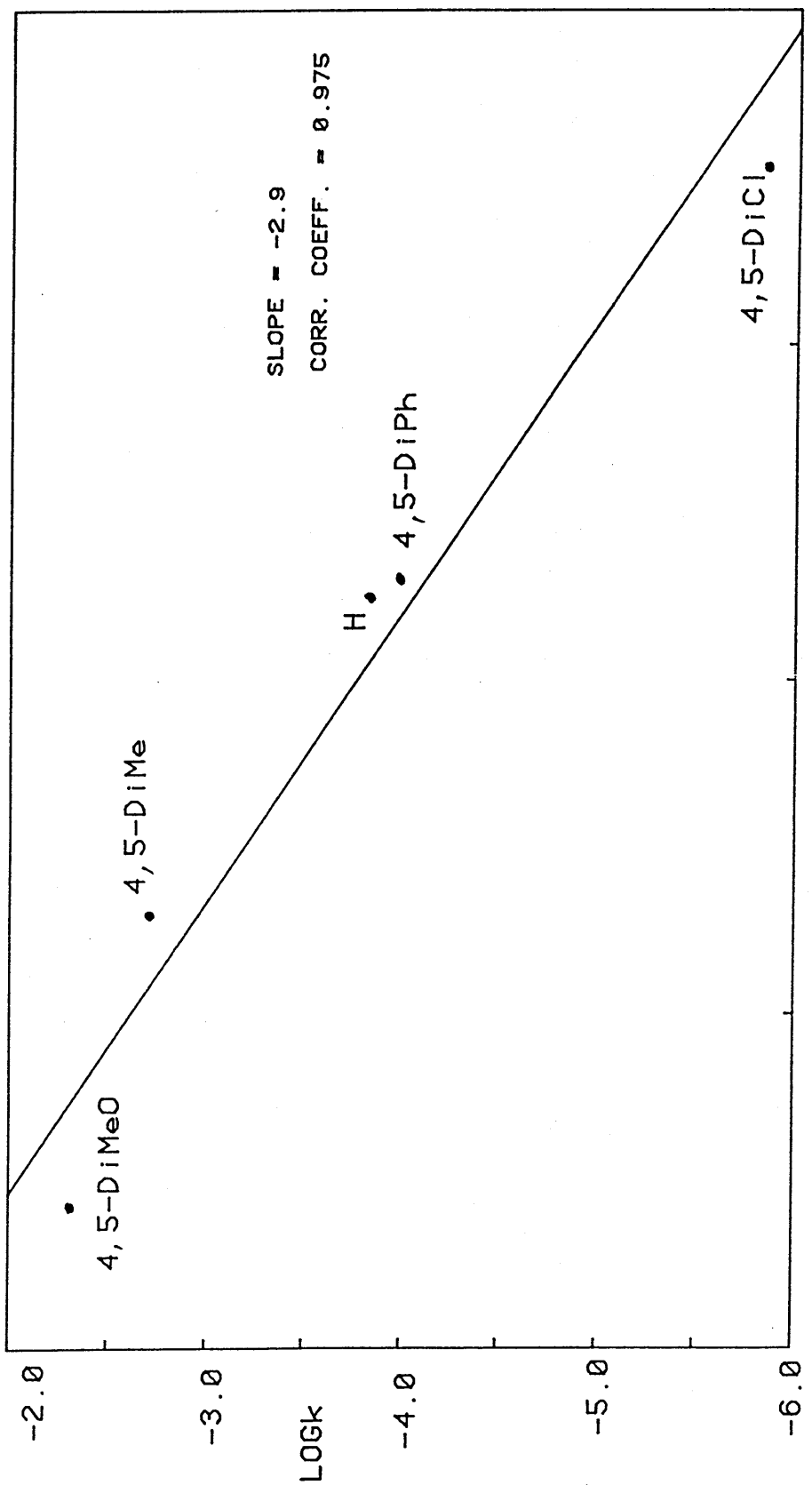


Fig. 3.56

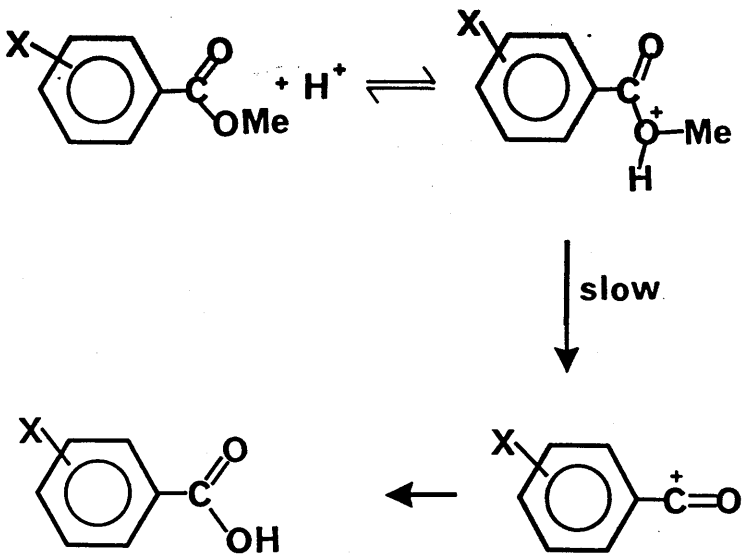
A ρ value of -2.93 (c.c. 0.975) was obtained for these compounds. The fact that 2(3-tolyl)-4,5-dimethoxybenzoic acid seems not to fit on the line generated by the other four compounds (slope -3.5, c.c. 0.99) could be attributed to hydrogen bonding involving the methoxy oxygens, this results in a lower rate of reaction than would be expected. Nevertheless a slope of -2.93 indicates a substantial build up of positive charge at the reaction site during the rate limiting step. This value compares very well with that of substitution reactions of benzyl halides where a ρ value of about -4 is produced.[40] The

PLOT OF LOGk (97% $MeSO_3H$) VS σ^+ FOR DISUBSTITUTED CPDS



(Fig. 3.55)

hydrolysis of benzoic acid esters by the $A_{AC}1$ mechanism



which involve the same rate limiting acylium ion formation to the reaction under study have a ρ value of -3.2 for 4-substituted,2,6-dimethylbenzoate esters[32] and a ρ value of -3.2 for the hydrolysis of 4-substituted methylbenzoates in 99.9% sulphuric acid.[41] Both of these results are in excellent agreement with the values calculated earlier, confirming similar mechanisms.

Knowing these ρ values, the slopes of log k vs H_o and the Arrhenius parameters (where necessary) it is possible to compare the rate of the reaction under study with electron donating substituents with that of ester hydrolysis by the $A_{AC}1$ mechanism. By using the plots of log k vs H_o to correct for the acid strength and the ρ value to correct for the extra substituents, the data in the paper of Chimiel and Long on the hydrolysis of methylmesitoate[31] predict that at H_o = -7.5 and 90°C the substituted benzylbenzoic acid should cyclise by rate limiting acylium ion formation with a rate constant of 2.42 s^{-1}. Arrhenius plots on 3-tolylbenzoic acid predict that at H_o = -7.5 and 90°C the compound should cyclise with a rate constant of 0.574 s^{-1} only a factor 4.2 slower than predicted. A similar treatment on the data obtained by Bender[42] on the same ester hydrolysis in stronger acid (H_o = -5.62) at

25°C again predicts a rate only a factor of 3 times faster than observed. This excellent agreement again confirms that both reactions proceed by the same rate limiting steps. The larger values predicted by the methylmesitoate hydrolysis could be a result of the larger steric effect of two ortho methyl groups. If this is the case hydrolysis of ethylbenzoate by the $A_{AC}1$ mechanism should predict a smaller rate constant. This is indeed so, treatment of the data of Edwards and Wong predicts a rate which is a factor of 12 times slower. Clearly the relief of steric strain encourages the reaction when ortho substituents are present.

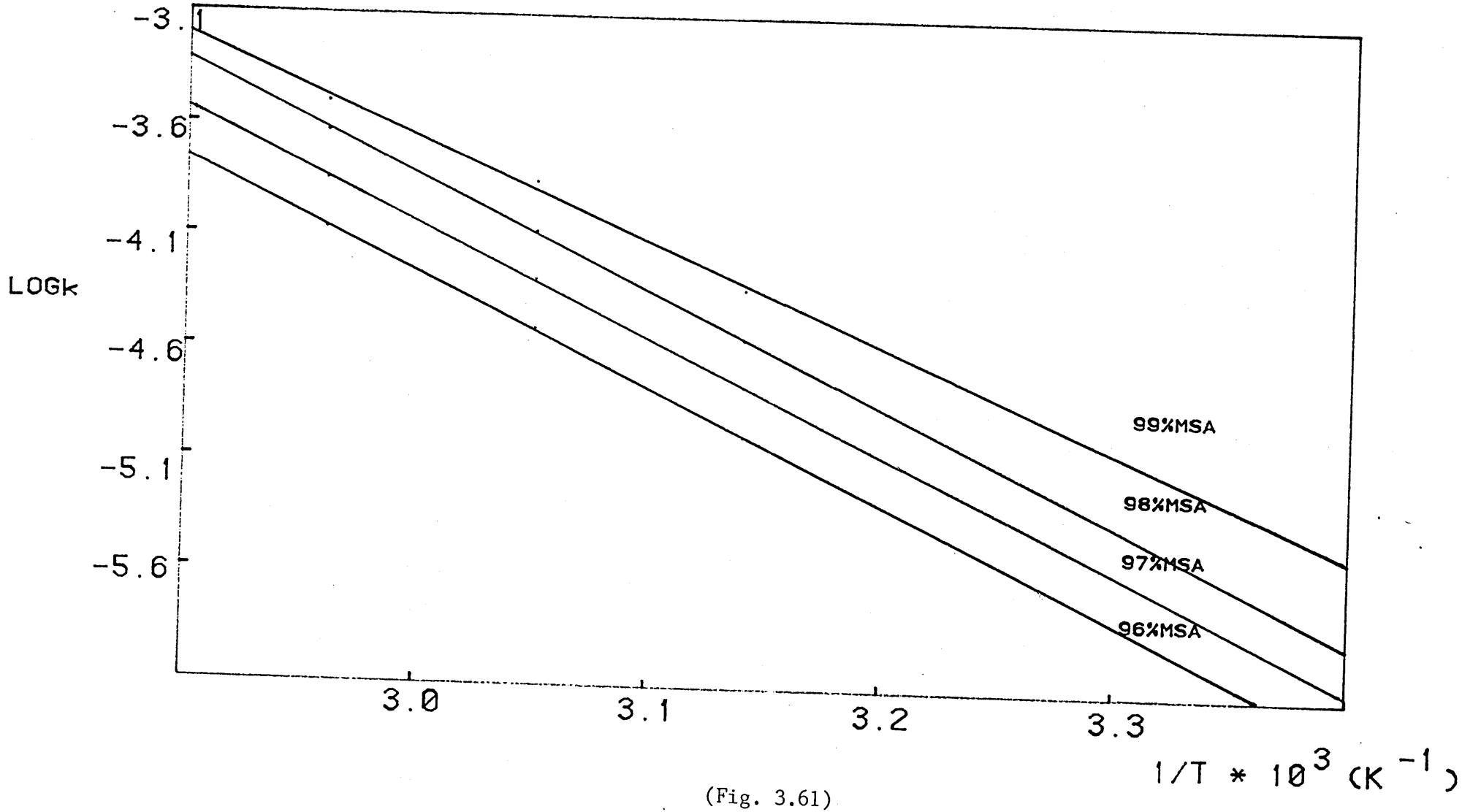
3.6 Activation Energies

Variable temperature studies allow the calculation of enthalpies and entropies of activation. These are shown together with those of related reactions in Table 3.61 and the associated Arrhenius plots shown in Figure 3.61 and 3.62.

Table 3.61 Activation parameters for various benzoic acid derivatives

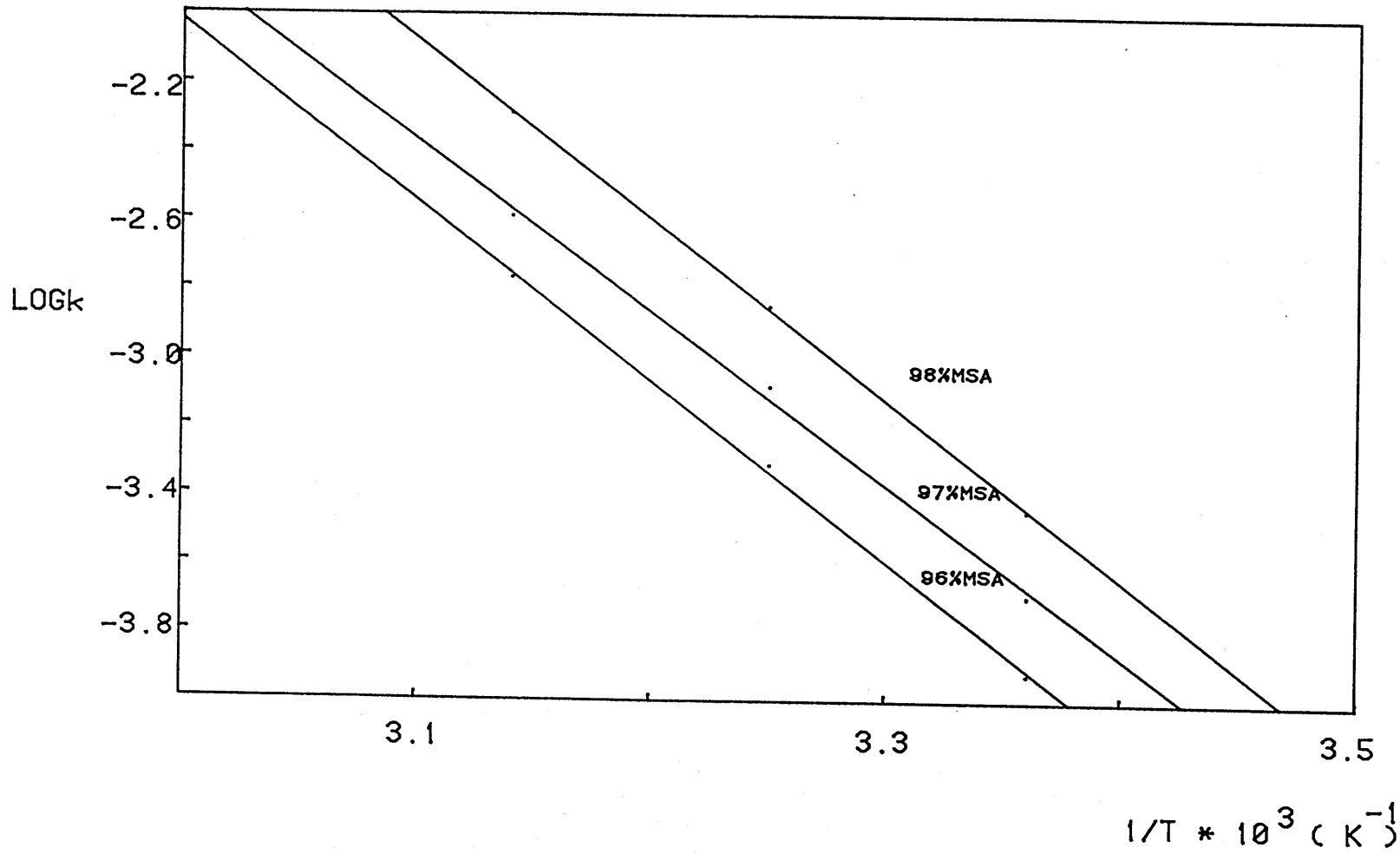
Compound	Ea/KJ	A/S^{-1}	$S^{\neq}$/J	$H^{\neq}$/KJ	Acidity
2(3-Tolyl)benzoic acid	101.8	2.6×10^{14}	+31.07	99.3	) 98%
2(3-Tolyl)4,5-dichloro-benzoic acid	97.3	2.6×10^{11}	-26.27	94.8	) MSA)
2-Benzoylbenzoic acid	129.58	1.42×10^{14}	25.98	127.1	84.54% H_2SO_4
2,2-Diphenic acid[a]	107.84	2.8×10^{11}	-26.76	105.34	83% H_2SO_4

a = Data read from Fig. 4 and 5 of D.M. March and T. Henshall, J. Phys. Chem., 66, 840 (1962).


ARRHENIUS PLOT OF LOGk VS 1/T FOR DICL CPD (XIV)
-3.
-3.6
-4.1
-4.6
-5.1
-5.6
LOGk
99%MSA
98%MSA
97%MSA
96%MSA
3.0
3.1
3.2
3.3
1/T * 10^3 (K^-1)

(Fig. 3.61)

ARRHENIUS PLOT OF LOGk VS 1/T FOR 3-Me CPD (II)



(FIG. 3.82)

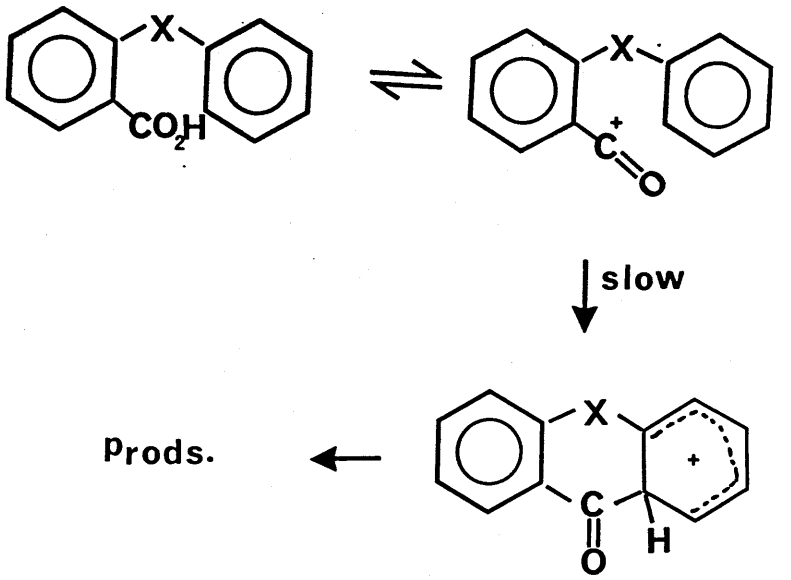
The cyclisation of 2(3-tolyl)benzoic acid has a reasonable $H^{\neq}$ and a positive $S^{\neq}$. These compare very well with those obtained in the hydrolysis of methylmesitoates, $H^{\neq}$ = 102.3 $KJmol^{-1}$ and $S^{\neq}$ = $40JK^{-1}mol^{-1}$. Both entropies of activation are positive because there is less constraint on the reaction system in the transition state which is in the process of losing a molecule of water.

If the rate depended on a step involving the formation of a cyclic compound there would be a reduction in entropy so a negative entropy of activation may be expected. This is the case with diphenic acid indicating that cyclisation may be kinetically significant in this instance. The cyclisation of 2(3-tolyl)-4,5-dichlorobenzoic acid has a negative entropy of activation, indicating that cyclisation may be kinetically significant. The slopes of log k vs H_o for this compound, however, indicates that the third step is rate limiting. Both the dichloro and the unsubstituted tolylbenzoic acids fit on the Hammett plot for substituents in the benzoic acid ring which shows no evidence for a change in mechanism. This apparent paradox may be the result of the large errors associated with Arrhenius plots carried out over a moderate temperature range, but will require, nevertheless, further investigation.

3.7 Comparison Between the Cyclisation of Benzoylbenzoic Acids and Benzylbenzoic Acids

Figure 3.7 shows a Hammett plot for the benzoylbenzoic acids substituted in the benzoyl ring. Whilst there is a good deal of scatter a large ρ value is obtained, in good agreement with that obtained for the benzylbenzoic acid series with electron withdrawing substituents. This confirms that for both these systems cyclisation is

kinetically important (Scheme 3.71).



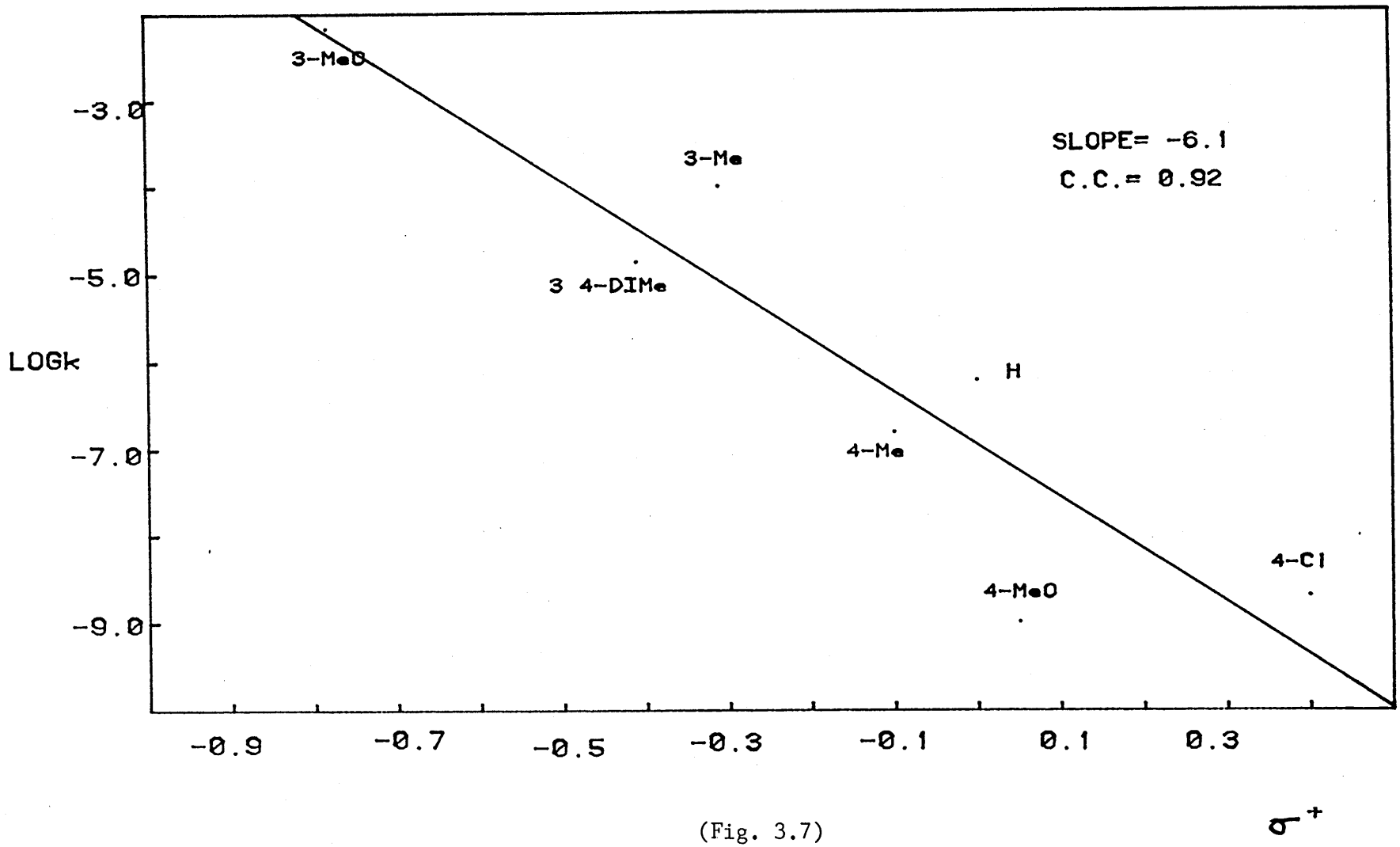
Scheme 3.71

Presumably the replacement of the CH_2 group by a C=O group ($\Delta\sigma^+ = 0.8$) ensures that the aromatic moiety does not compete successfully with water for the carboxonium ion.

Where protonation of the substrate is not significant log k for the benzoylbenzoic acids seems to follow H_R rather than H_o (slope against H_R is 0.92) again indicating equilibrium acylium ion and water formation. Indeed despite the many assumptions it was possible to estimate quite accurately the effect of replacing a CH_2 group by a C=O group, assuming a common mechanism (section 3.4). The only differing result for the benzoylbenzoic acid series is that it has a positive entropy of activation (Table 3.61) where we might expect a negative value as observed in the diphenic acid case.

To conclude, both series of substrates seem to proceed by similar mechanisms, the presence of the C=O group only becoming kinetically significant at high acidity when the protonated species and the lactol carbonium ion are formed in significant amounts.

PLOT OF LOGk vs σ^+ FOR VARIOUS 2-BENZOYLBENZOIC ACIDS WITH SUBSTITUENTS IN THE BENZOYL RING



(Fig. 3.7)

3.8 Product Studies on the Cyclisation of 2-Benzylbenzoic Acids

All the compounds prepared for kinetic studies were also cyclised separately in methanesulphonic acid and the products characterised. The method used for cyclisation has already been given in the experimental section. All the compounds were cyclised in 100% methanesulphonic acid for ten half-lives and the products characterised using ^{1}H and ^{13}C nmr spectroscopy (Table 3.80a and b). 2(3-Fluorobenzyl)benzoic acid was further investigated with ^{19}F and 400 MHz ^{1}H nmr spectroscopy (Table 3.80c). In the ^{19}F spectrum a sextet was observed at 105.991ppm (with respect to trichlorofluoromethane). This was due to two ortho-hydrogens coupling to give a triplet (J = 8.4 Hz) and being further split by a meta hydrogen to give two triplets (J = 5.7 Hz), thus showing that during cyclisation electrophilic attack took place para to the fluoro substituent. Further verification of this product was obtained by the oxidation of the anthrone by chromium trioxide to the anthraquinone. This enabled comparison of melting point and nmr data recorded in the literature.[43,44,45] This oxidation and comparison was also carried out on cyclised products of 2(3-methoxybenzyl)benzoic acid, 2(3-chlorobenzyl)benzoic acid and 2(3-tolyl)benzoic acid.[43,44,45] Product studies on 2-(2-deuterobenzyl)benzoic acid were discussed in section 3.3. The results of these studies are summarised in Table 3.81.

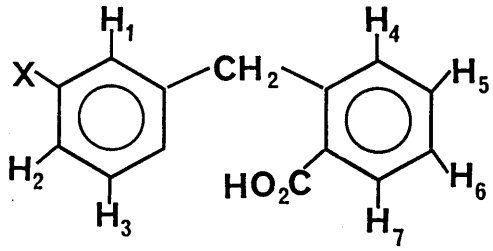
Table 3.80a ^{1}H nmr data on cyclodehydration products of monosubstituted benzylbenzoic acids

Compound cyclised	Nmr data on cyclised compound	
	Aromatic ^{1}H data (δ)	Alkyl ^{1}H data (δ)
2(3-Tolyl)benzoic acid	8.30-8.18(M,2H) 7.58-7.19(M,5H)	4.28,4.24(2S,2H) 2.83,2.41(2S,3H)
2(3-Methoxybenzyl)benzoic acid	8.30-8.16(M,2H) 7.49-7.27(M,3H) 6.92-6.73(M,2H)	4.09(S,2H) 3.78(S,3H)
2(3-Chlorobenzyl)benzoic acid	8.36-8.18(M,2H) 7.60-7.31(M,5H)	4.24(S,2H)
2(3-Fluorobenzyl)benzoic acid	8.44-8.27(M,2H) 7.65-7.02(M,5H)	4.29(S,2H)
2(4-Tolyl)benzoic acid	8.31-8.15(M,2H) 7.51-7.34(M,5H)	4.26(S,2H) 2.43(S,3H)
2(4-Methoxybenzyl)benzoic acid	8.21(M,1H) 7.73(M,1H) 7.44(M,5H)	4.16(S,2H) 3.81(S,3H)
2(4-Chlorobenzyl)benzoic acid	8.20-8.18(M,2H) 7.56-7.24(M,5H)	4.16(S,2H)
2(4-Fluorobenzyl)benzoic acid	8.33-7.26(M,7H)	4.28(S,2H)

Table 3.80b ^{1}H nmr data on cyclodehydration products of trisubstituted benzylbenzoic acids

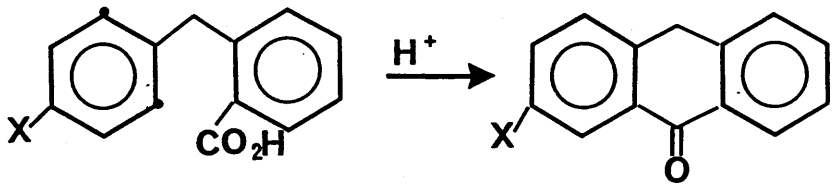
Compound cyclised	Nmr data on cyclised product	
	Aromatic ^{1}H data (δ)	Alkyl ^{1}H data (δ)
2(3-Tolyl)-4,5-dimethyl-benzoic acid	8.26-8.06(M,2H) 7.24-7.13(M,3H)	4.11(S,2H) 2.40(S,3H) 2.30(S,6H)
2(3-Tolyl)-4,5-dimethoxy-benzoic acid	8.25-8.16(D,1H) 7.75(S,1H) 7.30-7.17(M,2H) 6.77(S,1H)	4.13(S,2H) 3.97-3.94(D,6H) 2.41(S,3H)
2(3-Tolyl)-4,5-diphenyl-benzoic acid	8.40-8.22(M,2H) 7.48-7.19(M,13H)	4.31(S,2H) 2.43(S,3H)
2(3-Tolyl)-4,5-dichloro-benzoic acid	8.38-8.16(M,1H) 7.56-7.26(M,4H)	4.27,4.23(2S,2H) 2.82,2.45(2S,3H)

Table 3.80c 400 MHz ^{1}H nmr data on the cyclodehydration of



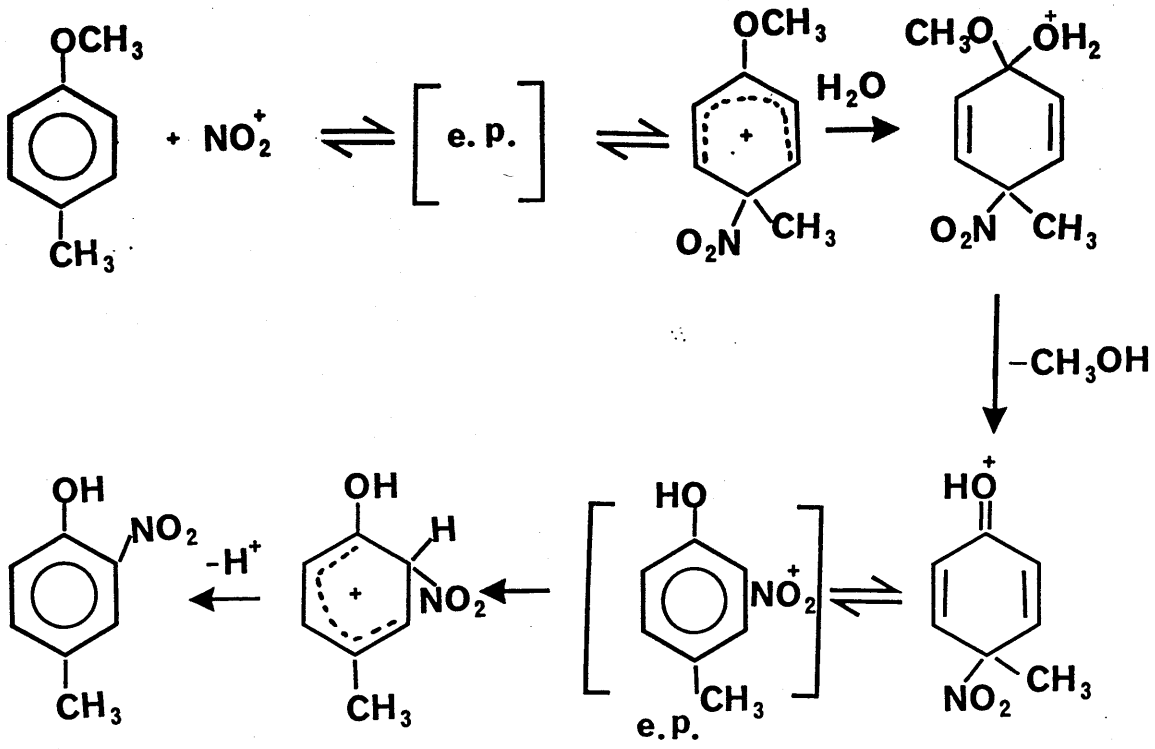
	^{1}H nmr data on product of cyclodehydration (δ)						
X	H_1	H_2	H_3	H_4	H_5	H_6	H_7
OMe	6.8260-6.8197, (M)	6.9515-6.9451, 6.9295-6.9233, (2D)	8.2787-8.2548, (D)	7.3859-7.3617, (M)	7.4237-7.3995, (M)	7.5397-7.5344, 7.5194-7.5157, 7.5008-7.4970, (3D)	8.3189-8.3158, 8.2994-8.2960, (2D)
F	7.1575-7.0968, (M)		8.3894-8.3178, (M)	7.4702-7.4221, (M)		7.6002-7.5965, 7.5816-7.5778, 7.5628-7.5591, (3D)	8.3894-8.3178, (M)

As can be seen from Table 3.81, the 4-substituted benzylbenzoic acids gave the expected product. In this case only two possible positions of attack are available (other than ipso) and both lead to the formation of the same product, (Scheme 3.81).



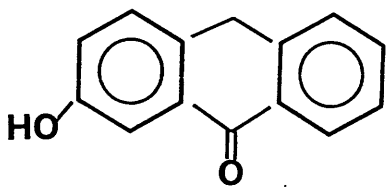
Scheme 3.81

In the cyclodehydration of 2(4-methoxybenzyl)benzoic acid the question of demethylation through ipso substitution arose. A number of references where such behaviour is observed have been cited in the literature. M.V. Sargent[46] has reported the formation of a cyclohexadienone derivative through ipso substitution followed by demethylation in a Friedel-Crafts acylation reaction, (see p47). In the nitration of p-methylanisole one of the products identified was 4-methyl-2-nitrophenol, the proposed mechanism for this is shown in Scheme 3.82.[47]



Scheme 3.82

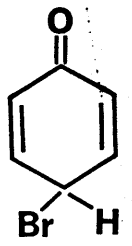
A similar mechanism is proposed by C.L. Perrin and G.A. Skinner[48] for the nitration of 4-chloro-anisole in which 4-chloro-2-nitrophenol was observed. If ipso substitution was occurring in the cyclodehydration of 2(4-methoxybenzyl)benzoic acid through a similar mechanism the product obtained should be a phenol (I).



I

However, no such demethylation was observed the only product being 3-methoxyanthrone in 97% yield.

In a recent paper O.S. Tee et al.[49] have reported the observation of the unstable intermediate 4-bromo-2,5-cyclohexadienone (II) in the aqueous bromination of phenol and similar results have been obtained by other workers in nitration reactions.[50-53]



II

In the cyclodehydration of 2(3-hydroxybenzyl)benzoic acid and 2(4-hydroxybenzyl)benzoic acid no evidence was found for a cyclohexadienone intermediate. All the kinetic runs were well behaved and all the ultraviolet spectra passed through one isobestic point.

For compounds with a substituent in the 3-position of the benzyl ring only two possible isomers can be formed (other than by ipso attack). However, only 2(3-tolyl)benzoic acid produced two isomers. This compound was also cyclised in varying acidities of methanesulphonic acid (93-100%). All studies, however, revealed the same product isomer distribution.

The remaining compounds giving (within experimental error) only the corresponding para substituted product. Table 3.82 lists ortho-para ratios for other electrophilic aromatic substitutions.

Table 3.81 Data on the products of cyclisation of benzylbenzoic acids in 100% methanesulphonic acid.

Compound	Temperature °C	% of isomers formed[b] Ortho[a]	Para[a]	Meta[a]
2-Benzylbenzoic acid	25°C	-	-	-
2(3-Tolyl)benzoic acid	25°C	25	75	-
2(3-Methoxybenzyl) benzoic acid	25°C	-	100	-
2(3-Chlorobenzyl) benzoic acid	25°C	-	100	-
2(3-Fluorobenzyl) benzoic acid	25°C	-	100	-
2(3-Hydroxybenzyl) benzoic acid	25°C	-	100	-
2(4-Tolyl)benzoic acid	25°C	-	-	100
2(4-Methoxybenzyl) benzoic acid	25°C	-	-	100
2(4-Chlorobenzyl) benzoic acid	25°C	-	-	100
2(4-Fluorobenzyl) benzoic acid	25°C	-	-	100
2(4-Hydroxybenzyl) benzoic acid	25°C	-	-	100
2(3-Tolyl)-4,5-dimethyl benzoic acid	25°C	-	100	-
2(3-Tolyl)-4,5-dimethoxy benzoic acid	25°C	-	100	-
2(3-Tolyl)-4,5-diphenyl benzoic acid	25°C	-	100	-
2(3-Tolyl)-4,5-dichloro benzoic acid	65°C	37.5	62.5	-

a = These positions are with respect to the position of substituent in the benzyl ring.
b = Determined by the nmr technique, values quoted have an error of ±5%.

Table 3.82 Ortho, para and meta % isomer distributions for various electrophilic substitution reactions on benzene derivatives

Substituent	Benzylation[a]			Nitration[b]			Bromination[c]			Chlorination[d]		
	O	M	P%	O	M	P%	O	M	P%	O	M	P%
OH	54	-	46	52	-	48	10	-	90	50	-	50
OMe	48	-	52	57	-	42	4	-	96	21	-	79
Me	48	-	52	61	3.7	31	32.9	0.3	66.8	59.8	0.48	39.7
F	19	-	81	13	0.6	86	10.7	0.2	89.1	-	-	-
Cl	32	2	60	35	1	64	10.7	0.1	89.2	39	6	55

a - J. Blackwell and W.J. Hinkinbottom, J.C.S. 366 (1963).
b - OH from Aromatic Nitration, K. Schoefield, Cambridge Univ. Press, P245 (1980);
Me from J.W. Barnett et al., J. Chem. Soc. Perkin II, 648 (1975);
OMe from J.W. Barnett et al., J. Chem. Soc. Perkin II, 248 (1977);
Cl and F from R.G. Coombes et al. J. Chem. Soc. 13, 347 (1961).
c - OMe from B. Jones and E.N. Richardson, J. Chem. Soc. 3939 (1956);
OH, F and Cl from D.H. Derbyshire and W.A. Wates, J. Chem. Soc. 564 (1950);
Me from H.C. Brown and L.M. Stock, J. Am. Chem. Soc., 79, 1421, 5175 (1957);
d - OH from A.F. Holleman, Chem. Rev. 1, 187 (1925);
Cl and F from L.N. Ferguson et al., J. Amer. Chem. Soc., 76, 1250 (1954); see also P.B.D. Le Mare, J. Chem. Soc., 4450, (1954);
Me from P.B.D. Le Mare and M. Hassan, J. Chem. Soc., 3004 (1957); see also P.B.D. Le Mare et al., J. Chem. Soc., 2756 (1958);
OMe from P.B. De La Mare and C.A. Vernon, J. Chem. Soc., 1764 (1951).

In agreement with our results the methyl substituent gives the highest o/p ratio. This is because all the other groups are inductively withdrawing. The inductive effect decreases with distance from the substituent deactivating the ortho position most and the para position least. The results with electron donating groups confirm that despite the lack of "substrate selectivity" arising from a change in rate limiting step a large positional selectivity is maintained.

It is feasible that product formation in the cyclodehydration of 2-benzylbenzoic acids may have been influenced by steric effects. For example, with a bulky substituent one may expect reaction to occur mainly para to it, whereas a small substituent should give reasonable quantities of both ortho and para substituted compounds. However, this was not found to be the case, and the opposite trend was observed. The small fluoro group gave only the one isomer with substitution para to the fluoro group. The larger methyl group gave both ortho and para substituted compounds.

A limited amount of work has been done characterising the products of the cyclisation of 2-benzoylbenzoic acids.[54] Noyce and Kittle found that the cyclisation of 2(3-methoxybenzoyl)benzoic acid in concentrated sulphuric acid results in only one product being formed, namely 2-methoxyanthraquinone. This is in agreement with our results. Our studies on the products of cyclisation of 2(3-toluoyl)benzoic acid in concentrated sulphuric acid show the formation of both ortho and para substituted isomers in the ratio of 1:3.4 respectively. Again this result mirrors that discussed earlier for 2(3-tolyl)benzoic acid. This compound was also cyclised in methanesulphonic acid of varying concentrations ranging from 92% - 100%. In each case, however, the same product isomer distribution was found.

A similar system to ours, 2-benzylbenzaldehydes, has also been studied in both sulphuric and methanesulphonic acid and the products of cyclisation characterised.[55] The results of this study are reproduced below in Table 3.83. As can be seen from the data the results are in agreement with ours.

Table 3.83 Data on the products of cyclisation of benzyl-benzaldehydes in 100% methanesulphonic acid.

Compound	Temperature °C	% of isomers formed[b]		
		Ortho[a]	Para[a]	Meta[a]
2-Benzylbenzaldehyde	25°C	-	-	-
2(3-Tolyl)benzaldehyde	25°C	40	60	-
2(3-Methoxybenzyl) benzaldehyde	25°C	-	100	-
2(3-Chlorobenzyl) benzaldehyde	25°C	-	100	-
2(3-Fluorobenzyl) benzaldehyde	25°C	-	100	-
2(4-Tolyl)benzaldehyde	25°C	-	-	100
2(4-Methoxybenzyl) benzaldehyde	25°C	-	-	100
2(4-Chlorobenzyl) benzaldehyde	25°C	-	-	100
2(4-Fluorobenzyl) benzaldehyde	25°C	-	-	100

a = These positions are with respect to the position of substituent in the benzyl ring.
b = Determined by the nmr technique values quoted have an error of ±5%.

The introduction of substituents in the benzoic acid ring allowed some control over the reactivity of the electrophile. With methoxy, phenyl,

or methyl substituents the electrophile was expected to be more stable than the unsubstituted molecule and therefore less reactive. According to the Reactivity-Selectivity Principle this means that in these cases the electrophile should be more selective. This was clearly borne out by the experimental results. Despite the fact that each compound contains a methyl group in the 3 position of the benzyl ring, only one isomer was found in each case. As discussed earlier the 2(3-tolyl)benzoic acid formed two isomers. Clearly the introduction of electron donating groups in the benzoic acid ring did indeed lead to a less reactive and more selective electrophile in accord with the Reactivity-Selectivity Principle.

With electron withdrawing substituents in the benzoic acid ring the reverse situation should be observed, that is, the electrophile will be destabilised thereby making it more reactive and less selective according to the Reactivity-Selectivity Principle. To test this 2(3-tolyl)-4,5-dichlorobenzoic acid was cyclised in methanesulphonic acid. As expected its rate of cyclodehydration was very slow indeed at room temperature, hence the kinetic measurements were carried out at 65°C and 45°C. This low rate of reaction was caused by the introduction of two chloro groups meta and para to the benzoic acid group, thereby making the molecule more acidic and less easy to protonate. Product studies at 65°C showed the presence of two isomers of methyl-6,7-dichloroanthrone. The ratio was closer to the statistical 1:1 ratio expected for an unselective reagent.

Clearly electron withdrawing groups in the benzoic acid ring destabilises the electrophile making it more reactive and less selective.

The question of reversibility was also investigated in this work, but no evidence was found for it. 2(3-Tolyl)benzoic acid was allowed to cyclise in methanesulphonic acid for 20 and 30 half-lives, but the products found in each case were the same ratio as those from ten half-life studies. Also samples were taken after one half-life, again the same ratio of products was obtained. Therefore no evidence of reversibility was observed. 1-Methoxyanthrone and 2-methoxyanthrone were also subjected to 100% methanesulphonic acid for twenty to thirty half-lives, but on examination of the products no rearrangement had occurred.

Since electron donating groups cause the third step to be rate limiting it was not possible to calculate the partial rate factor for substitution in the meta and para positions of a methyl substituent and hence test whether this system agreed with the Stock-Brown selectivity relationship.[56]

$$\text{Log } p_f = c \log (p_f/m_f)$$

where c 1.3-1.4

However, since for electron withdrawing substituents this system correlated well with σ^+ for both 3 and 4 substituted compounds one would expect that

$$\text{Log } p_f = (\sigma_p^+/\sigma_p^+-\sigma_m^+)S_f = 1.3S_f$$

in accord with the Stock-Brown relationship. This is confirmed by the benzylbenzaldehyde series where there is no change in the rate limiting

step and p_f and m_f for the methyl substituent can be calculated using the unsubstituted compound as the reference. In this case c = 1.24. One explanation for the curved Hammett plot is a switch from rate limiting σ complex formation to rate limiting π complex formation on going from electron withdrawing to electron donating substituents. Such an explanation has been proposed by Fountain to explain a similar curvature obtained in the acylation of aromatic substrates with ketenes.[57] However, the rates of π complex formation would not be completely insensitive to substituents in the aromatic ring. Electron donating substituents, particularly OMe etc., would increase the electron density increasing the rate of π complex formation. Low values of -2.567 obtained for vinyl cation alkylation,[58] -0.92 and -1.07 for dimethyl ketene acylation[57] have been explained in terms of π complexes. However, it is very difficult to reconcile the very low value obtained in this study with any kind of π complex involving the benzyl moiety.

In the system under study and the benzylbenzaldehyde series, substrate selectivities, where they can be measured, are high together with positional selectivity, giving no evidence for π complex formation in agreement with recent work by DeHaan[59] on Friedel-Crafts benzylation reactions. However positional selectivity does change with the reactivity of the electrophile indicating that the position of the transition state may vary, but always resembles a σ complex.

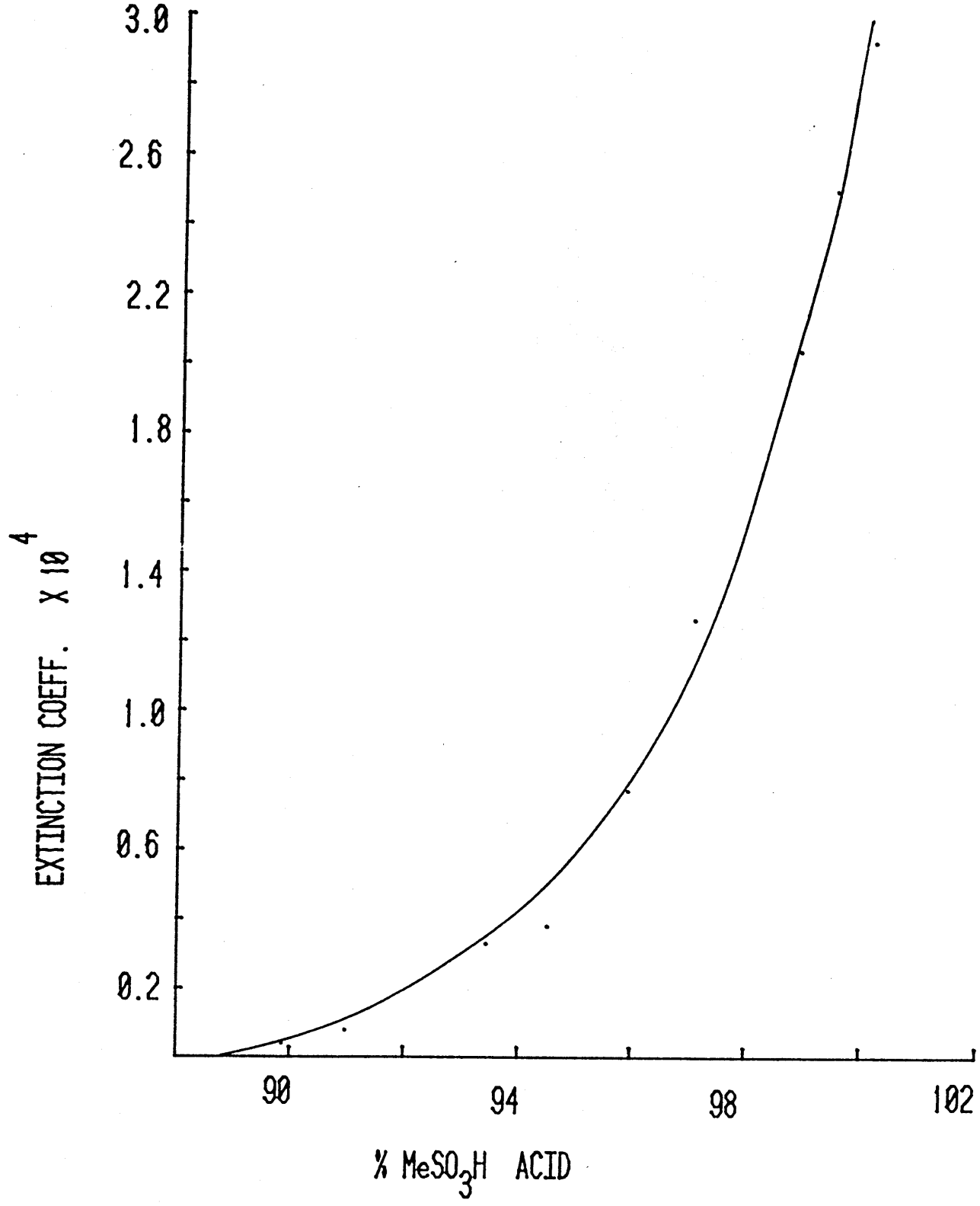
3.9 H_R Acidity Function Studies

Three indicators were employed in an attempt to obtain H_R acidity function data in the range 92% to 100% methanesulphonic acid (MSA). In

one case it was possible to obtain Log I values, however, since it was not possible to overlap these with any existing scale absolute H_R values were not calculated. Since Log I for the indicators chosen is proportional to H_R these values were employed in all subsequent plots.

The first indicator used was 2,2'-dimethylbenzhydrol. This indicator decomposes with time when mixed with methanesulphonic acid. Therefore each study was timed from the moment of mixing until the start of the ultraviolet fixed wavelength study. The absorbence scan was recorded over a period of ten minutes and the initial absorbence obtained by extrapolation. All measurements were made at 25.0°C and 455nm. The relevant data is given in Table 3.91. As can be seen from the plot of extinction coefficient against % methanesulphonic acid (Fig. 3.91) the indicator is not completely protonated in 100% methanesulphonic acid. As a means of determining the extinction coefficient after complete protonation, the stronger acid trifluoromethanesulphonic acid (TFMSA) was employed. Both mixtures of trifluoromethanesulphonic acid and methanesulphonic acid, and pure trifluoromethanesulphonic acid were used, but as can be seen from the results they were inconclusive. Next mixtures of methanesulphonic acid and methanesulphonic anhydride (MSAA) were used, but again the results proved to be negative. Deno obtained a value of 2.0×10^4 for the extinction coefficient of the corresponding diaryl carbonium ion in sulphuric acid.[60]

PLOT OF EXTINCTION COEFF. VS % $MeSO_3H$ ACID
FOR 2 2 - DIMETHYLBENZHYDROL INDICATOR



(Fig. 3.91)

Table 3.91 pK_a study data on 2,2'-dimethylbenzhydrol in methanesulphonic acid.

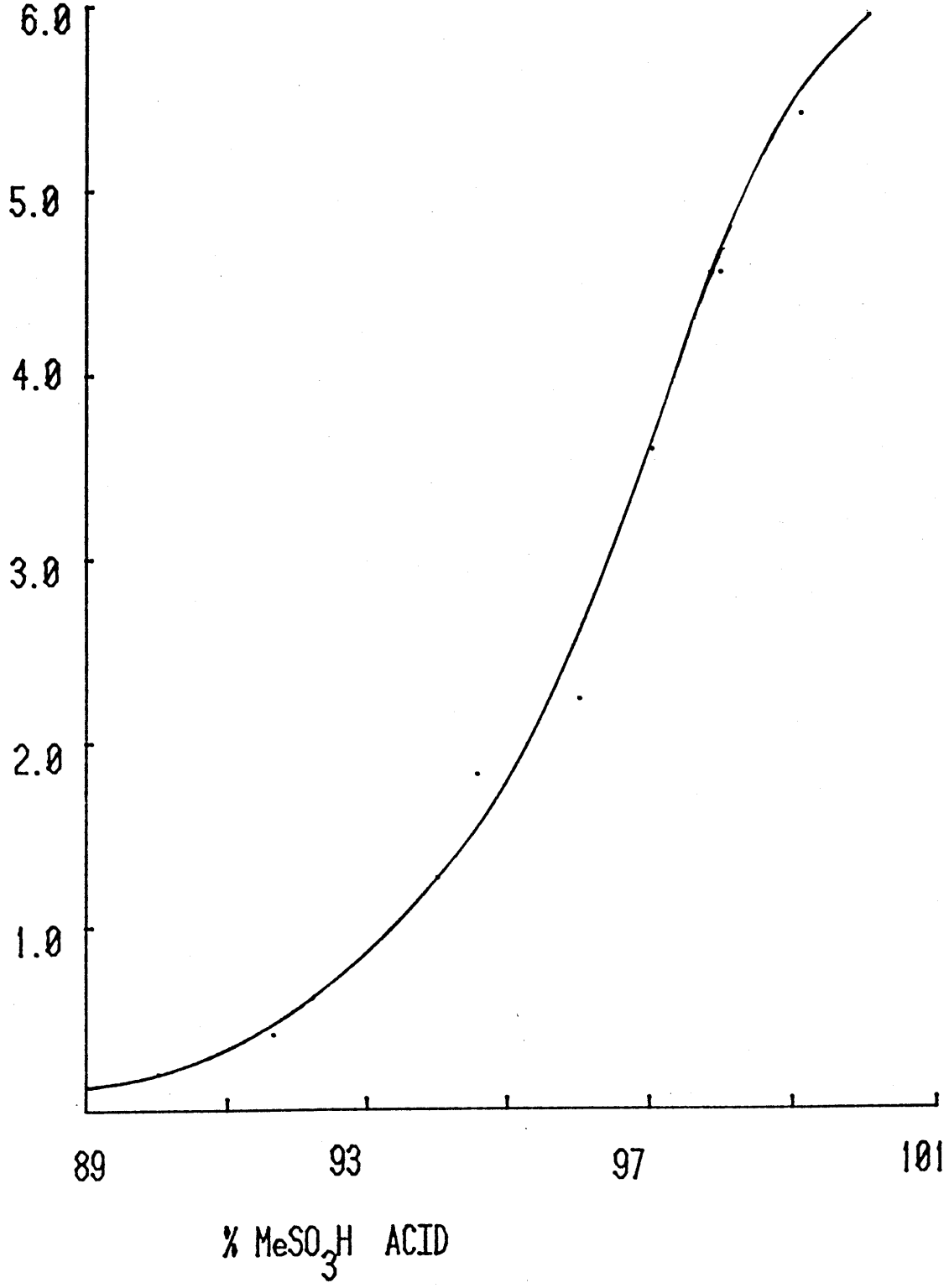
% Methanesulphonic Acid	Extinction Coefficient,[a], $x10^4$
100	2.917
99.39	2.491
98.80	2.03
97.03	1.157
95.89	0.766
94.50	0.378
93.43	0.326
89.86	0.041
90.97	0.079
50% TFMSA	1.43
100% TFMSA	3.855
12.61% MSAA	1.264

a - average of two readings

The second indicator used was 4-methylbenzhydrol. This also decomposed in methanesulphonic acid and therefore exactly the same procedure was employed to determine the extinction coefficient on mixing. All ultraviolet measurements were made at 25.0°C and 450nm.

Again the results proved to be inconclusive (Table 3.92), a good sigmoidal curve could not be obtained when the extinction coefficient was plotted against % acid (Fig. 3.92). The indicator was again not quite basic enough and complete protonation-dehydration was not possible even at 100% methanesulphonic acid. To overcome this

PLOT OF EXTICTION COEFF. VS % $MeSO_3H$ ACID
FOR 4 - METHYLBENZHYDROL INDICATOR



(FIG. 3.92)

difficulty methanesulphonic anhydride was added to 100% MSA, however, as can be seen from the result, even less protonation-dehydration seemed to be taking place in this mixture.

Table 3.92 pK_a study data on 4-methylbenzhydrol in methanesulphonic acid

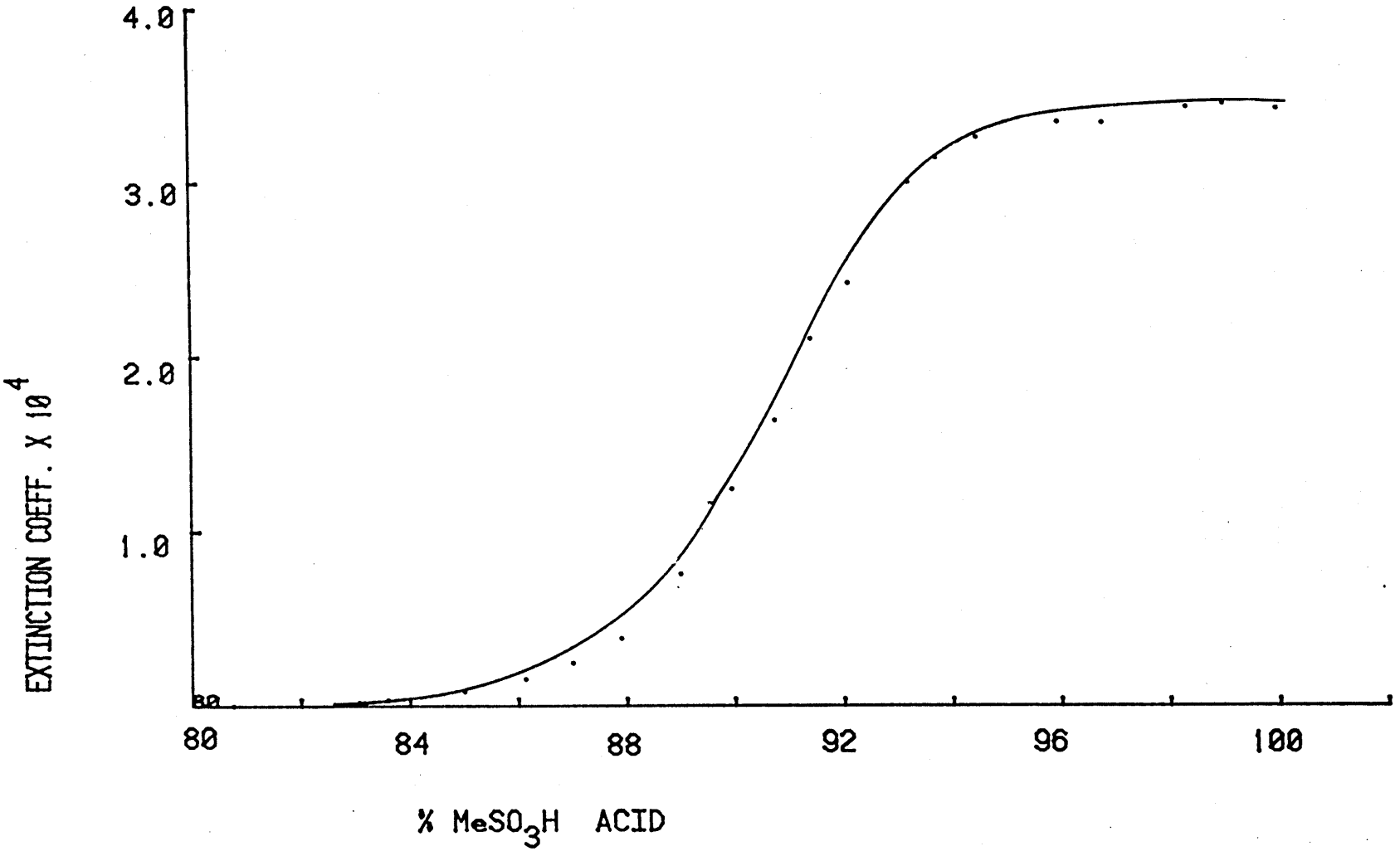
% Methanesulphonic Acid	Extinction coefficient,[a] x10^4
100.00	5.93
99.06	5.40
97.95	4.54
97.00	3.58
95.99	2.23
94.56	1.82
94.01	1.26
91.66	0.41
90.03	0.196
15% MSAA	3.95

a - average of two readings

The third indicator, 3,3',3"-trichlorophenyl carbinol proved to be the best indicator of the three. It did not decompose in methanesulphonic acid and produced excellent results (Table 3.93 and Fig. 3.93). The only drawback with this indicator was that it was not quite basic enough, being only valid in the region 87-94% methanesulphonic acid. Ultraviolet measurements were made at 25.0°C and 412nm. Log I values were obtained as described in the experimental (Table 3.94) and a plot

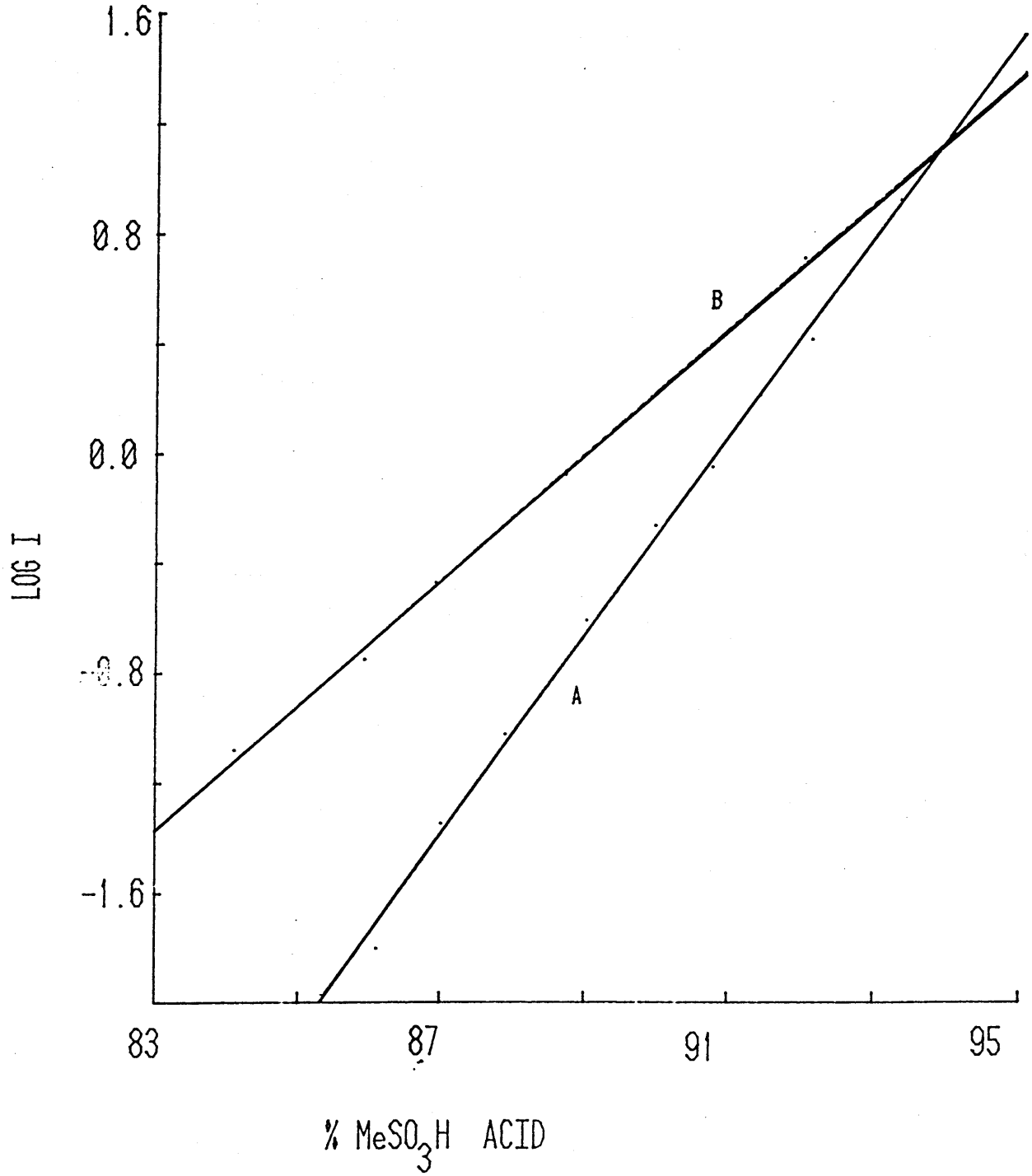
of log I against % methanesulphonic acid is given in Fig. 3.94. It is interesting to compare these log I values with those obtained by Barnett et al.[61] If the two indicators follow the same acidity function then when the two sets of data are plotted on the same axis two parallel straight lines should be obtained. In practice, however, the two lines have differing slopes (Fig. 3.94). 4-Methylbenzhydrol has a slope of 0.22 (B) whereas 3,3',3"-trichlorotriphenyl carbinol gives a slope of 0.36 (A). Mindl and Vecera[62] have defined an acidity function H_R for diphenylmethyl carbinols. They found that the slopes of log I vs % acid were smaller for the diphenyl carbinols than the triphenylcarbinols in agreement with our results in methanesulphonic acid. The main reason for the different slopes can probably be attributed to the different activity coefficients displayed by the two indicators used. The differing data poses problems for anyone wishing to use it in the elucidation of acid catalysed reaction mechanisms. Which set of data is the correct one to use? This can only be answered by further work on the system. Until that time, however, we shall use the 3,3'3"-trichlorophenyl carbinol data because it was used in the definition of H_R in sulphuric acid and thus provides a comparison with other reaction kinetics which have been measured in sulphuric acid.

PLOT OF EXTINCTION COEFF. VS % MeSO H ACID FOR TRIARYLCARBINOL



(Fig. 3.93)

PLOT OF LOG I VS %$MeSO_3H$ ACID FOR TWO DIFFERENT INDICATORS



(FIG. 3.94)

Table 3.93 pK_a data on 3,3',3"-trichlorophenyl carbinol in methanesulphonic acid.

% Methanesulphonic Acid	Extinction coefficient, $x10^4$
100.00	3.41
99.02	3.44
98.34	3.42
96.81	3.33
95.98	3.34
94.49	3.25
93.73	3.13
93.22	2.99
92.11	2.42
91.40	2.10
90.74	1.63
89.95	1.24
89.00	0.75
87.89	0.38
87.00	0.24
86.14	0.15
85.00	0.078
83.60	0.031
83.07	0.020
80.75	0.001

Table 3.94 Ionization ratios of 3,3',3"-trichlorophenyl carbinol in methanesulphonic acid.

% Methanesulphonic Acid	I (=B^+/BOH)	Log I	H_o
94.50	35.11	1.545	-7.12
93.30	8.29	0.918	-6.92
92.11	2.57	0.410	-6.74
91.40	1.61	0.208	-6.62
90.74	0.884	-0.054	-6.42
89.95	0.54	-0.267	-6.36
89.00	0.246	-0.609	-6.18
87.89	0.0943	-1.025	-5.96
87.00	0.045	-1.350	-5.79
86.10	0.0157	-1.804	-5.62

3.10 Studies in Magic Acid and Trifluoromethanesulphonic acid

In order to shed light on any carbonium ions that were being formed in the cyclodehydration of 2-benzylbenzoic acids, 2(2,6-dimethyl benzyl)-benzoic acid (Fig. 3.101) was prepared, and its reactions in Magic Acid and trifluoromethanesulphonic acid were studied using nmr spectroscopy.

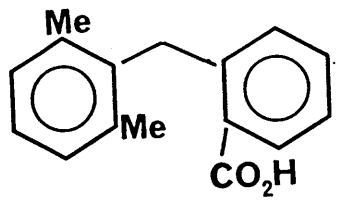
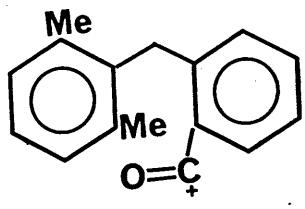


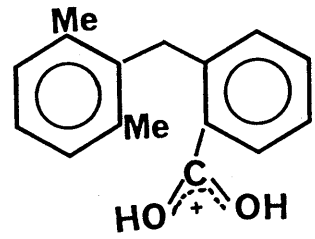
Fig. 3.101

A solution of 2(2,6-dimethylbenzyl)benzoic acid was prepared using fluorosulphuryl chloride at -70°C. To this was added a few drops of Magic Acid and its spectrum recorded still at -70°C. The solution was prepared under an atmosphere of nitrogen.

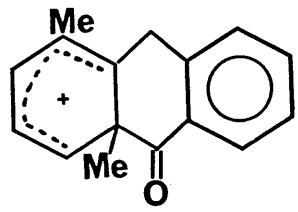
A number of changes could be clearly seen in these spectra. In the proton nmr the peaks were considerably broader and two methyl groups were no longer producing one signal; two signals were obtained for the methyl group. Evidence for the presence of such as I, II or III is conflicting, such that it is not possible to deduce which species predominates under these conditions.



I

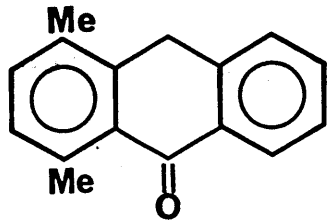


II

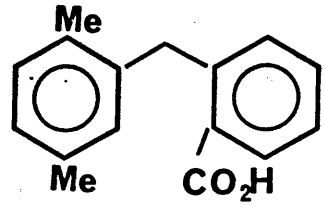


III

However, these spectra, and that of the reaction mixture after quenching, shows the presence of some IV and V.



IV

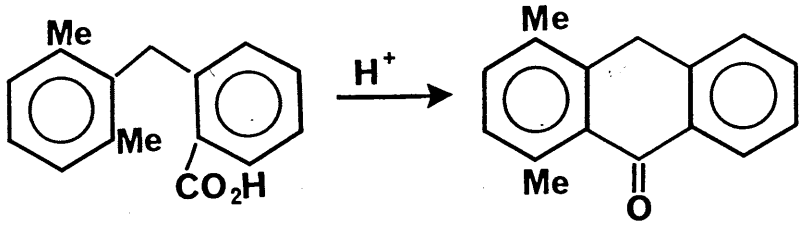


V

V is probably formed by protodeacylation of IV, a process which occurs readily with sterically crowded acylaromatics.[63]

The same mixture was also analysed using esr spectroscopy. This again was carried out at -60°C and strong evidence for the presence of an unpaired electron was obtained. It was, however, not possible to assign a structure to the species present or to say what its concentration was.

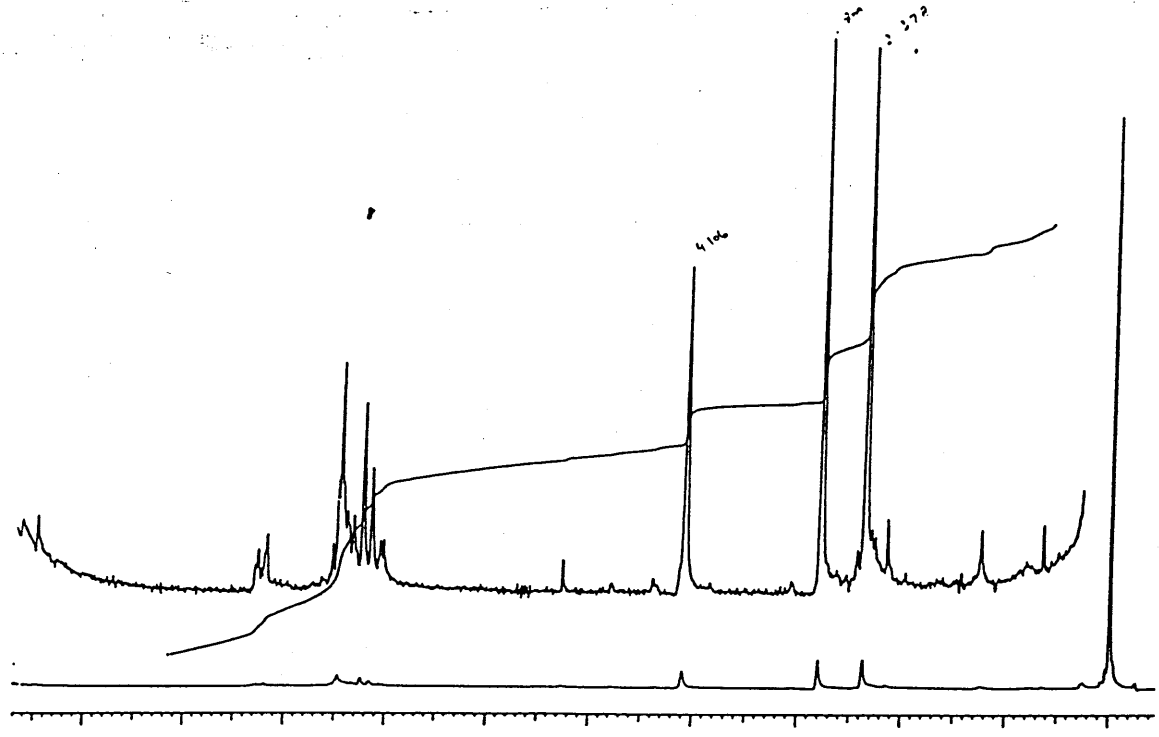
Studies in a mixture of trifluoromethanesulphonic acid and sulphur dioxide at -23°C also revealed similar spectra to those in Magic Acid solutions. At room temperature, however, ipso substitution took place to yield only one compound (Scheme 3.102), whereas with Magic Acid a complex mixture was obtained. Ipso substitution was very fast and the compound obtained was identified using nmr spectroscopy. In methanesulphonic acid however no reaction could be observed.



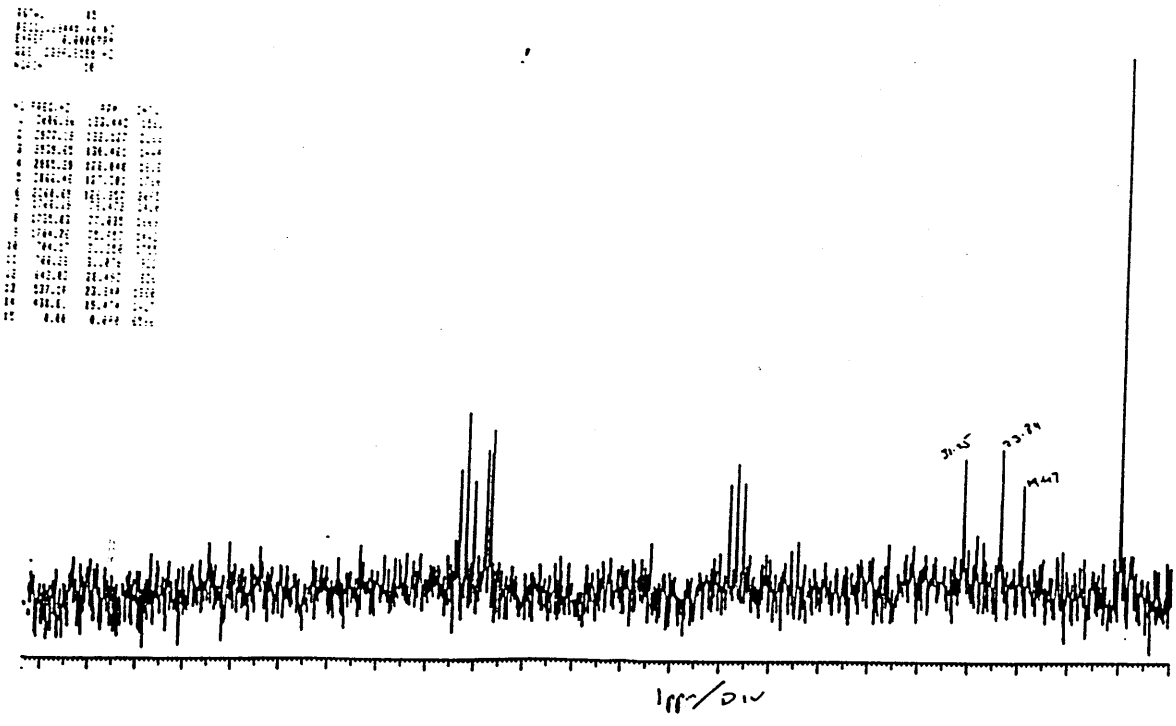
Scheme 3.102

The following data was obtained from ^{1}H spectrum δ 8.288 - 8.201 (1H,M), 7.541 - 7.043 (5H,M), 4.106 (2H,S), 2.809 (3H,S), 2.378 (3H,S). Some of these spectra have been reproduced overleaf.

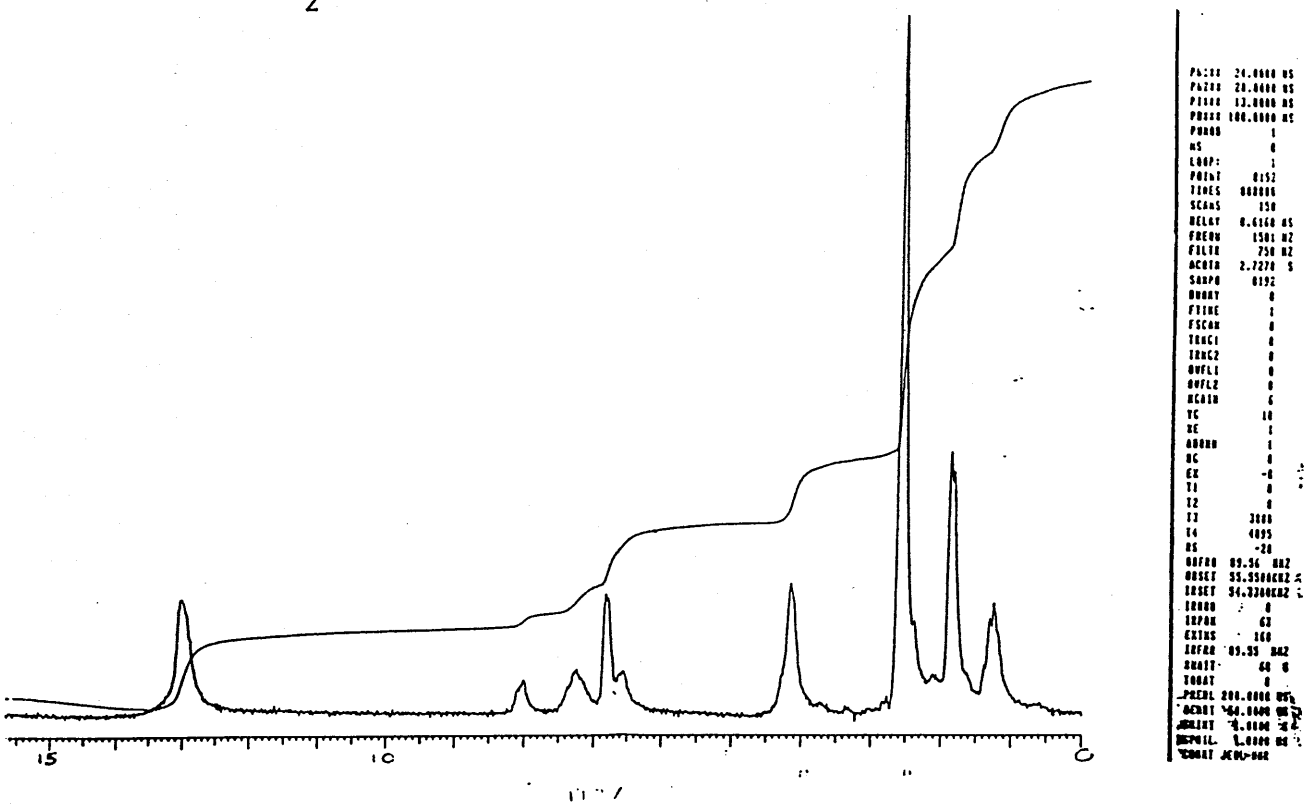
^{1}H nmr of the products of cyclisation 2(2,6-dimethylbenzyl)benzoic acid from trifluoromethanesulphonic acid.



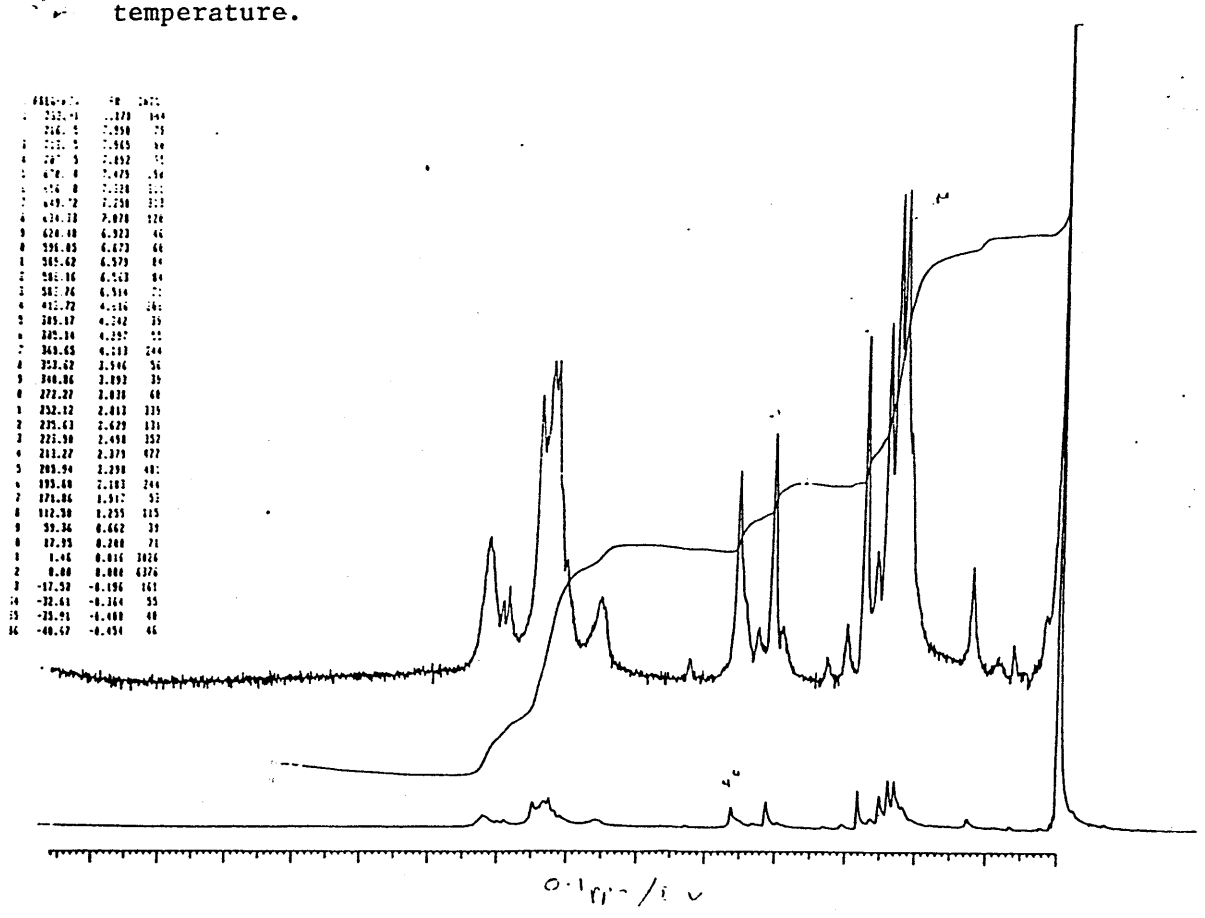
^{13}C nmr of the same products as above.



^1H nmr of 2(2,6-dimethylbenzyl)benzoic acid in a solution of Magic Acid and FSO_2Cl at -60°C.



^1H nmr of the products of the above reaction worked up at room temperature.



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